Risk factors for atrial fibrillation incidence and progression

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INTRODUCTION

Atrial fibrillation (AF) affects millions of people worldwide, and numbers are expected to increase.(1) It is estimated that by the year 2060 the prevalence of AF will have doubled compared to present numbers, meaning that over 3% of the Dutch population aged ≥55 years (547,700 individuals) will have AF. AF has a large impact on the individuals' life, and is accompanied with symptoms and impaired quality of life.(2) It is a progressive disease, resulting in an increased risk of stroke, dementia, heart failure and mortality, and causes increasing health care expenses.(2-4)

However the epidemiology of AF is changing. This is related to the ageing population, but also in part with improvements in treatment of hypertension, myocardial infarction and heart failure; changing lifestyle; increasing awareness of AF in patients and health-care professionals; and improvements in non-invasive detection of AF.(5)

In therapeutical decision making for AF symptoms take a central place. However the relation of symptoms with AF temporal patterns, underlying disease and outcome is poorly understood. It is also becoming apparent that sex related differences exist in AF risk factors, symptoms and the risk of cardiovascular events.(6,7) Little is known about the underlying pathophysiological mechanisms. Progression of AF involves atrial remodeling, increased AF chronicity and occurrence of cardiovascular events. (8) This continuum of AF progression may be affected by changes in AF risk factors. Therefore, it is of utmost importance to keep track of ongoing changes in risk factors for AF incidence, progression and outcome, to provide better risk management in AF.

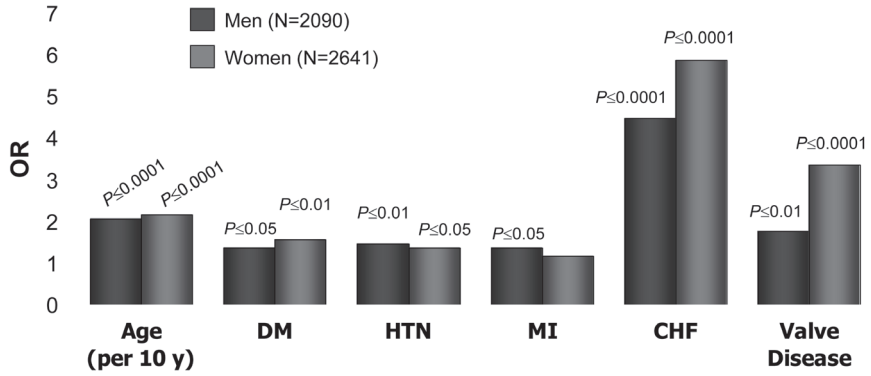
RISK FACTORS FOR INCIDENT AF

Current knowledge on the incidence, prevalence and risk factors of AF is predominantly based on cohorts that were initiated long time ago.(9-12) Traditional risk factors for AF include advancing age, hypertension, heart failure, coronary artery disease, diabetes mellitus and valve disease (**Figure 1**).(9) Data from the Framingham Heart Study suggests that obesity has become increasingly important as a risk factor for incident AF in recent years, while the risk associated with traditional risk factors has decreased with better treatment. (5) Although many risk factors for AF have been described, only part of the risk for incident AF is explained (C statistic 0.76), even if obesity is taken into account.(13)

There is a considerable amount of research reporting on other novel AF risk factors besides obesity, including borderline hypertension, left ventricular diastolic dysfunction, left atrial dilatation, obstructive sleep apnea syndrome, excessive exercise or lack of physical activity, and alcohol abuse.(14-17) Notably, many of these novel risk factors

are lifestyle related, and may contribute more to AF risk in younger persons than the traditional AF risk factors (**Figure 2**).(18)

Pathophysiological mechanisms relating novel risk factors to incident AF are diverse. These include hemodynamic mechanisms such as increased filling pressures, which lead to atrial stretch and atrial dilatation, atrial fibrosis and ultimately AF.(9-11,13,19-24) Increased autonomic tone may be involved in obstructive sleep apnea syndrome, excessive exercise, vagal triggers and stress.(25,26) Inflammatory mechanisms are also involved, such as pro-inflammatory cytokines in obesity, leading to an inflammatory response in the atria, leading to atrial fibrosis and ultimately AF.(27-33) Recent work also showed that next to causing inflammation and fibrosis in the atrial myocardium, epicardial fat may also infiltrate the atrial myocardium, directly causing an AF substrate.(27,28) Both traditional and more novel AF risk factors may lead to atrial remodeling through these diverse mechanisms.(17) More research in contemporary patient populations is needed to further establish the contribution of novel AF risk factors, to ultimately improve AF risk prediction in present clinical practice.



95% CI						
Men	1.8-2.5	1.0-2.0	1.2-2.0	1.0-2.0	3.1-6.6	1.2-2.5
Women	1.9-2.6	1.1-1.2	1.1-1.8	0.8-1.8	4.2-8.4	2.5-4.5

2-Year pooled logistic regression

Figure 1. Traditional risk factors for incident atrial fibrillation in the Framingham Heart Study. Data obtained from (7).

Abbreviations: CHF = chronic heart failure; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction.

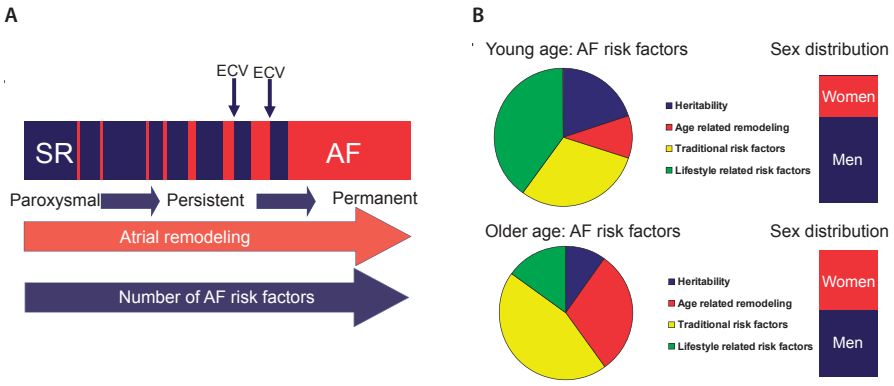


Figure 2. Conceptual figure of the association of AF progression with increasing atrial remodeling and increasing numbers of AF risk factors (**A**). Disitributions of AF risk factors and the proportion of men and women may differ between populations of younger and older AF patients (**B**). In younger patients (age <60 years) there may be a greater influence of lifestyle related risk factors and heritability, and the greatest part are men. In older patients (age >60 years), traditional risk factors for AF become more important, and the proportion of women increases.

SEX RELATED DIFFERENCES IN UNDERLYING DISEASE AND OUTCOME

Male sex is a well known risk factor for incident AF, independent of concomitant cardiovascular disease.(17) However it has been described that the proportion of women in AF populations increases with the age of the population.(34) This may be caused by the longer life expectancy in women in the general population, but may also be a consequence of differences in underlying diseases and risk factors in men and women with AF, causing differences in age of AF onset.(34-39)

Differences in AF risk factors exist between men and women, although exact data is sparse.(37) Men more often have coronary heart disease and heart failure with reduced ejection fraction (HFrEF). (6,39-42) Women more often have hypertension and heart failure with preserved ejection fraction (HFpEF), often at older age than men who develop heart failure.(6,39-42) Even within patients with HFpEF, women have more pronounced echocardiographic diastolic dysfunction, compared to men.(37,38)

Women with AF may also be at higher risk of adverse outcomes. It has been described that after the age of 65 years women are at higher risk of stroke independent of other stroke risk factors.(7,43) This has led to including female sex in the CHA_2DS_2VASc score, which is recommended by recent European and North American guidelines.(2-4) Recent data also shows that women with AF may be at higher risk of incident myocardial infarction and dementia, which, together with the increased risk of stroke, may reflect a common underlying pathophysiological mechanism.(44-47) No differences between men and women have been reported for the overall occurrence of heart failure, mortality or

bleeding during follow-up.(39,48-50) However, as discussed earlier, differences exist in the type of heart failure, with women having more often HFpEF.(6,48)

The mechanisms causing older women to be at increased risk of adverse outcomes, predominantly stroke, are not known. It has been described that postmenopausal women have increased signs of endothelial dysfunction with increased thrombogenic state, increased pulse pressure and worse blood pressure regulation than men, which might predispose women with AF to vascular events such as stroke, myocardial infarction and (vascular) dementia.(51) Next to relations with vascular events, endothelial dysfunction may also be a mechanism involved in development of HFpEF (rather than heart failure with reduced ejection fraction), which might be the reason why the HFpEF phenotype is more prevalent and more pronounced in women.(52-55) In the end, older women with AF may have a 'full house' of risk factors, including obesity, heart failure hospitalizations, diabetes and vascular disease, severely increasing the risk of stroke. Clearly, differences in sex distributions may cause differences in clinical profiles among AF populations. The exact nature of these differences however, needs to be further described.

PROGRESSION FROM PAROXYSMAL AF TO PERSISTENT AND PERMANENT AF AND RELATIONS WITH SYMPTOMATIC AF

Progression from paroxysmal AF to sustained forms of AF has been related to ageing, and increasing numbers and severity of underlying disease (**Figure 2**).(8,56-59) The HATCH scoring system calculates 1 point for hypertension, age ≥75 years, chronic obstructive pulmonary disease, and 2 points for transient ischemic attack or stroke, and heart failure. (8) The HATCH scoring system allows for instant classification of the risk of progression to persistent or permanent AF, allowing moderate predictive validity.(60,61) No differences in rate of progression from paroxysmal to persistent or permanent AF have been described between men and women.(8)

Symptoms and severity of symptoms vary widely within patients and between patients with AF,(62-67) and are known to vary according to temporal patterns of AF (paroxysmal, persistent, or permanent AF).(58,62,66) Palpitations, dyspnea, fatigue, chest pain and dizziness are most commonly described.(58,66,68)

Comorbidities such as heart failure, coronary heart disease and valvular disease, but also extra-cardiac comorbidities such as chronic obstructive pulmonary disease may present with similar symptoms or may aggravate existing symptoms.(62,69-71) Although paroxysmal AF often is highly symptomatic, it is associated with less underlying disease than persistent or permanent AF.(8,58,59,66,68,72) Conversely, persistent and permanent AF are often less symptomatic (or recognized as symptomatic) than paroxys-

mal AF, but are associated with more underlying disease, and hence more cardiovascular events.(8,58,59,66,68,72)

There may also be differences between the types of symptoms reported in paroxysmal, persistent and permanent AF. Paroxysmal AF patients may present with more palpitations, while complaints of dyspnea are more pronounced in patients with persistent or permanent AF.(59,68,72) **Figure 3** shows the association of symptom type with AF temporal patterns in three AF registries; the data reported from EORP-AF was collected at 1 year follow-up, (72) the other studies reported baseline data.(59,68) In another report from the EORP-AF study a prevalence of physician-assessed symptoms at baseline was 60.3%,(73) which is comparable to the prevalence after 1 year.(72) Data on the association of symptom type with AF pattern was provided only for the 1-year follow-up, but shows a similar relation of AF temporal patterns with the other studies. Although the ALFA study (68) was performed in the 1990s and the other studies were more contemporary, the mean age, assessment of symptoms (by the treating physician) and time from AF diagnosis were comparable. However, Realise AF had the highest proportion of patients with permanent AF (50%), compared to 17% in EORP-AF and 45% 'chronic AF' (combination of persistent and permanent) in the ALFA study.(59,68,72)

Symptoms of dyspnea and fatigue may less often be detected and recognized as AF related by the treating physician (causing the patient to be labeled asymptomatic),(74) but may be associated with more severe underlying disease in persistent and permanent AF compared to paroxysmal AF.(8,48,58,59,66,68,72) However the relation between AF symptoms and underlying disease has not been well established. In hospital-based registries involving heterogenous populations of AF patients, symptomatic AF assessed by the physician may be a marker of shorter AF episodes and hence less underlying disease.(73-75) But, on the other hand, among patients with comparable AF status and thus more comparable symptoms, presence of symptoms may also relate to more underlying disease.(62,70,71) This is supported by findings from an analysis in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study, showing that in a population with predominantly persistent AF, symptomatic AF patients had more coronary heart disease and heart failure.(62)

The vast majority of studies report symptoms as assessed by the treating physician. AF symptoms take a central role in current AF management, which is likely to have caused increased attention and awareness of AF symptoms by treating physicians.(76,77) Nevertheless a recent study showed that 11% of patients that were assessed as asymptomatic by the treating physician, reported mild symptoms using the Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT).(74) Assessment of symptoms may thus be further improved by allowing patients to fill out questionnaires on symptoms and quality of life. (39,70,71,78-81)

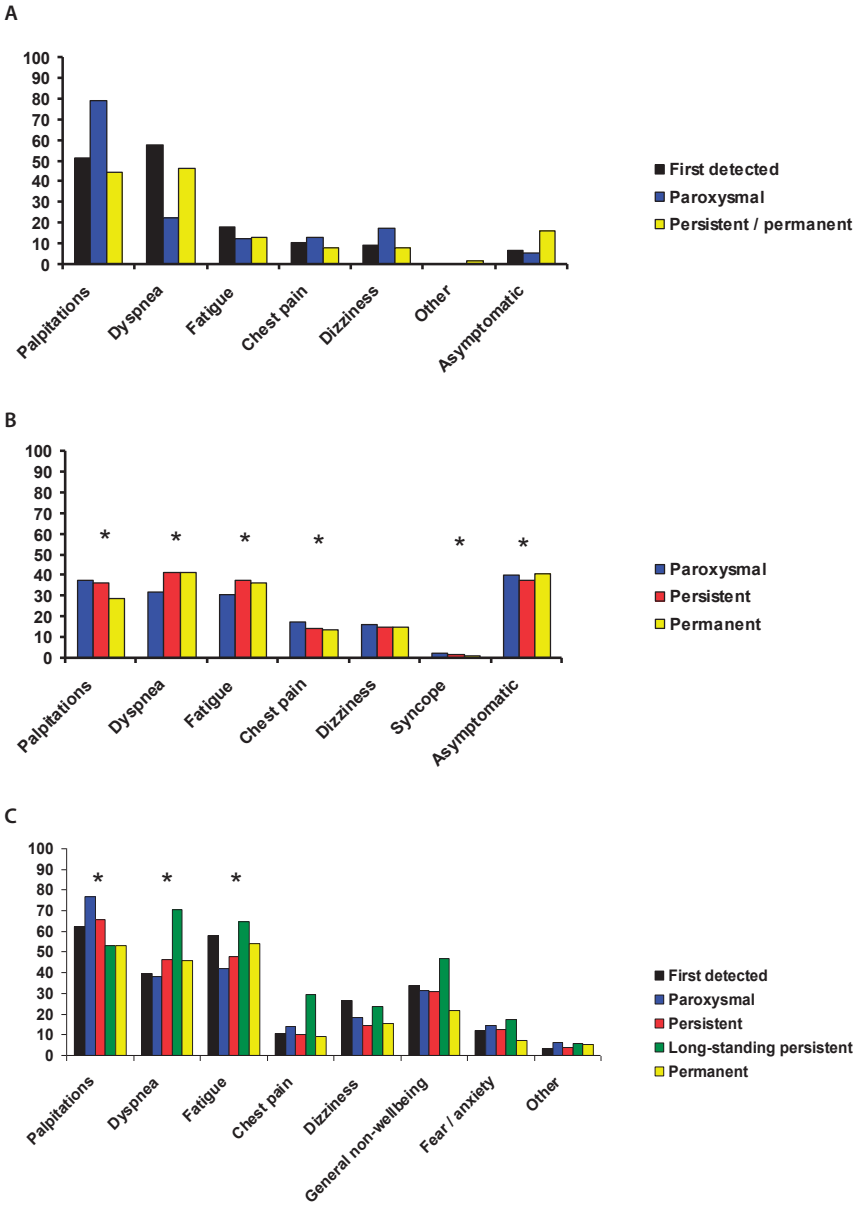


Figure 3. Prevalence of individual symptoms according to different clinical AF types in the ALFA study (68) (**A**), Realise AF study (59) (**B**) and EORP-AF study (72) (**C**). Palpitations are reported the most by paroxysmal AF patients. The proportion of patients reporting dyspnea and fatigue is higher in patients with persistent and permanent AF forms than in paroxysmal AF. *P<0.05. No P-values for the presented data were provided in the ALFA study.(68)

In previous analyses of the Rate Control Versus Electrical Cardioversion (RACE) and Rate Control Efficacy in Permanent Atrial Fibrillation II (RACE II) studies, women with respectively persistent and permanent AF were more symptomatic than men, and had more impaired quality of life.(39,70,71) This has also been shown in other studies.(62,66,68,73,74,82,83) In addition, women with persistent AF in the RACE study were reported to have more hypertension and heart failure hospitalizations, again suggesting a relation between symptoms, underlying disease and female sex.(39,42) Thus, differences in underlying disease, such as increased prevalence of HFpEF, may be one of the reasons why women with persistent and permanent AF are more symptomatic than men.(6,39,48,57,66,84) Establishing the clinical significance of symptoms within specific AF populations may provide additional measures of risk stratification in AF.

CHANGES IN AF TREATMENT WHICH MAY AFFECT PROGRESSION

Treatment of AF has significantly changed during the last fifteen years. The most important change has been lifelong use of oral anticoagulation in patients at risk for stroke irrespective of the present rhythm, reducing the risk of stroke.(85) Important improvements in oral anticoagulation have also been made in the last few years.(86-88) Nevertheless, stroke is still the most important AF related outcome.(2-4) Identification of patients truly at risk for stroke remains a challenge, since C-statistics of the widely used CHA_2DS_2VASc and $CHADS_2$ scores are <0.70, meaning that an important proportion of stroke risk remains unpredicted.(43,49,89,90) Next to reducing the risk of stroke, treatment with oral anticoagulation may cause serious bleeding events, so there will always be a need to optimize stroke and bleeding risk prediction schemes.(49,91) Also, adverse outcomes beyond stroke remain a significant problem, with heart failure and mortality being the most recognized adverse outcomes apart from stroke.(50)

As discussed previously, symptoms take a central role in guiding AF therapeutic decisions, since rhythm versus rate control trials have shown no benefit of either strategy in terms of outcomes,(92,93) and neither have strict or lenient rate control strategies.(71,94,95) Indeed, since the large rhythm versus rate control trials, rhythm control success has evolved rapidly, with catheter-based ablation strategies taking a central role in treatment of symptomatic AF patients. (3,4,76,96) Studies investigating whether modern rhythm control therapy in patients with early stages of AF may improve prognosis by preventing progression of the underlying AF substrate are underway.(85,97,98)

EFFECTS OF CHANGING LIFESTYLE ON ATRIAL FIBRILLATION EPIDEMIOLOGY

AF often occurs at advanced age, and most commonly in the presence of concomitant cardiovascular disease, although age itself has also been identified as a risk factor for AF.(17) Nevertheless AF is frequently encountered in young individuals under 60 years of age.(58,66) Incidence of AF in young individuals ranges between 0.17-3.8 per 1000 person years, and AF prevalence ranges from 0.03-1.46%.(99) However, the incidence may be increasing, due to changes in lifestyle, consumption pattern and lack of exercise, which may lead to early development of obesity and other cardiovascular conditions (**Figure 2**).(18,100) Younger individuals may be prone to a higher relative contribution of lifestyle-related risk factors for AF such as obesity, too little or excessive physical exercise, as well as to more genetic causes of AF.(17) Data on the exact causes of atrial fibrillation in younger individuals is sparse.(18)

Only until recent years there has not been much attention for lifestyle related AF risk factors. During the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference in 2011 obesity was still labeled as a less established AF risk factor, although increasing evidence was being found.(17) Body mass index, overweight, obesity and weight gain have all been associated with incident AF, independent of associated risk factors and conditions.(17) With the increasing prevalence of obesity in the community and the continuous improvement of treatment of cardiovascular disease, obesity is becoming increasingly important as an AF risk factor, while the importance of more traditional AF risk factors diminishes.(5,101) Recent research has shown that obesity may not only increase AF risk through shared risk factors, but also through direct pro-inflammatory and pro-fibrotic effects of epicardial adipose tissue on the atrial myocardium, and even through infiltration of the atrial myocardium by adipocytes, causing an AF substrate.(27-29,102,103) Interestingly, recent studies also showed that an aggressive strategy aiming on not only on weight loss, but also reduction of alcohol intake, treatment of obstructive sleep apnea syndrome, and, also of relevance, improvement of physical fitness resulted in reductions of AF burden and atrial remodeling, which offers a huge opportunity to treat modern AF patients and prevent AF progression.(30-32,104) Currently, inclusion in the Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (RACE 3) study is being finalized.(97) This study combines lifestyle management with an aggressive contemporary rhythm control approach including atrial ablation, aiming to improve rhythm control and prognosis in patients with early AF and heart failure.(85,97)

AIM OF THIS THESIS

Current knowledge on the epidemiology of AF stems from mainly North-American cohorts that were initiated a long time ago. However the epidemiology of AF is changing. This thesis focuses on uncovering associations of underlying disease with incident AF and AF progression in contemporary AF populations. It is increasingly becoming apparent that sex related differences exist in AF risk factors. Although this is not the focus of this thesis, we will investigate sex related differences where relevant. In **Chapter 2** we will investigate the incidence of AF in a contemporary community-based cohort study in the Netherlands. We will also investigate comorbidities associated with incident AF, and associations of incident AF with cardiovascular outcomes, including heart failure with both preserved and reduced ejection fraction. In **Chapter 3** we discuss the reciprocal relationship between AF and myocardial infarction, as described in recent studies. In **Chapter 4**, we will describe risk factors for AF in young patients aged <60 years, compared to older AF patients, age ≥60 years, and compared to healthy controls. Asymptomatic AF is often not recognized until AF related complications arise. However in patients with comparable AF temporal patterns receiving treatment for AF, absence of symptoms may relate to less underlying disease,(62) and thus better outcomes. In **Chapter 5** we will compare symptomatic recurrent persistent AF in the RACE study to asymptomatic AF, and investigate whether differences exist in underlying disease and progression to adverse outcomes. Likewise, in **Chapter 6**, we will investigate whether severity of AF symptoms, quantified with the AF severity scale,(79) impacts cardiovascular outcome in permanent AF. Finally, atrial remodeling is a marker of AF progression. Current data suggests that obesity, an important but modifiable risk factor for AF in current AF populations, causes atrial remodeling in AF patients. Atrial function is known as a marker of atrial remodeling, and impaired atrial remodeling may precede atrial dilatation, making it a sensitive early marker of remodeling.(105) In **Chapter 7** we will investigate the relation between obesity and left atrial function, measured with echocardiographic strain analyses. Ultimately, we will summarize the results of this thesis in **Chapter 8**, and put the results in perspective.

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PART I

Risk factors for atrial fibrillation incidence

Chapter 2

Incidence of Atrial Fibrillation and Relation with Cardiovascular Events, Heart Failure and Mortality – A Community-Based Study from the Netherlands

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ABSTRACT

Background.

Important improvements have been made in treatment of diseases associated with atrial fibrillation (AF), e.g. hypertension, myocardial infarction and heart failure. Incidence rates and risk factors may have changed with the ageing of the population and changing lifestyle. Currently, the risk for AF is only partially explained, possibly due to differences between older cohorts and contemporary populations.

Objectives.

We investigate the incidence of AF in a contemporary cohort study in the Netherlands, together with comorbidities associated with AF and associations of AF with cardiovascular outcomes.

Methods.

Incident AF was ascertained for hospital- and study electrocardiograms in 8265 participants of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study in Groningen, The Netherlands.

Results.

During 9.7 ± 2.3 years of follow-up, 265 participants developed AF, resulting in overall AF incidence of 3.3 per 1,000 person years. Advancing age, male sex, antihypertensive drug use, higher body mass index, previous myocardial infarction and previous stroke were associated with AF. After multivariable adjustment, AF was associated with cardiovascular events (hazard ratio 2.24 [1.06-4.75], $p = 0.035$), heart failure with either reduced or preserved ejection fraction (hazard ratio 4.52 [2.02-10.09], $p < 0.001$), and all-cause mortality (hazard ratio 3.02 [1.73-5.27], $p < 0.001$).

Conclusion.

Incidence of AF in the present cohort was comparable to data of older studies. Obesity has become a major risk factor for incident AF. While overall event rates were lower in the present study, the present study confirms the association of incident AF with cardiovascular events.

INTRODUCTION

Atrial fibrillation (AF) affects millions of people worldwide, and numbers are expected to increase (1). AF has large impact on the individual's life. It is accompanied by symptoms, impaired quality of life, increased risk of stroke, dementia, heart failure, mortality, and increasing health care expenses (2,3).

Multiple comorbidities have been associated with incident AF (1). However current knowledge on AF incidence, prevalence, risk factors and associated cardiovascular morbidity and mortality is based on predominantly North-American cohort studies that were initiated a long time ago, or more-recently registries based on questionnaires or ICD discharge codes (5-10). In recent years important improvements were made in pharmacological and non- pharmacological treatment of associated diseases, such as hypertension, myocardial infarction and heart failure (11-13). In addition, incidence rates and risk factors may have changed with the ageing of the population and changing lifestyle. Nowadays, the risk for incident AF is only partially explained, which may be due to differences between older cohorts and more contemporary populations. We investigate the incidence of AF, comorbidities associated with AF, and the associations of AF with cardiovascular events, systolic and diastolic heart failure and all cause mortality in the Dutch community-based Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort study.

METHODS

Population.

The PREVEND cohort study was founded in 1997 by inviting all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (n = 85,421) (14). Of all invitees, 40,856 responded (47.8%). Individuals with urinary albumin excretion (UAE) > 10 mg/L (n = 7,768) in their morning urine as well as a randomly selected control group with a UAE < 10 mg/L (n = 3,394) were invited to the PREVEND outpatient clinic. After excluding individuals with insulin-dependent diabetes mellitus, pregnant women, and individuals unable or unwilling to participate, a final cohort of 8,592 individuals was included and completed the baseline-screening program. The baseline-screening program consisted of 2 outpatient visits to assess demographics, anthropometric measurements, cardiovascular and metabolic risk factors, health behavior, and to collect blood samples and two 24-hour urine samples on 2 consecutive days. Participants were seen at 3-year intervals in the PREVEND outpatient clinic. For the present analysis, we excluded participants without any electrocardiogram (ECG) (n = 248) as well as participants with prevalent AF at the baseline screening (n = 79), leaving 8,265 participants. The PREVEND study was

approved by the institutional medical Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Assessment of AF.

Incident AF was diagnosed if either atrial flutter or AF was present on a 12-lead ECG obtained at 1 of the 3 PREVEND follow-up visits, or at an outpatient visit or hospital admission in the 2 hospitals in the city of Groningen (University Medical Center Groningen and Martini Hospital). A standard 12-lead ECG was performed at each PREVEND follow-up visit. All ECGs were digitally stored, and electronically screened for the following criteria: PR interval absence, atrial flutter, or ectopic atrial rhythm. This method of electronic screening was validated with complete manual screening by 2 independent observers of all ECGs from PREVEND baseline visit, and 100% sensitivity for the detection of AF or atrial flutter was reached. All ECGs determined via the electronic screening with suspected AF were manually reviewed by 2 independent observers. When an inconsistency was found or when both observers agreed on the diagnosis of AF or atrial flutter, the ECGs were validated by 2 independent cardiologists (**Figure 1**). Incident AF was diagnosed in 265 participants. For the date of incident AF the date of the first ECG with a definite diagnosis of AF or atrial flutter was used.

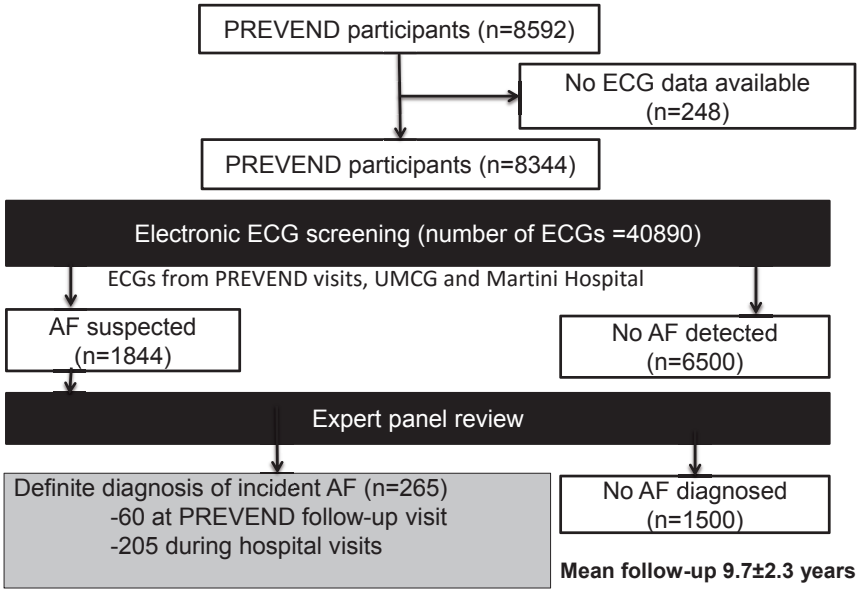


Figure 1. Atrial fibrillation ascertainment in PREVEND study.

Flow-chart of atrial fibrillation assessment in PREVEND study participants, using electrocardiograms made during PREVEND study visits and hospital visits.

Abbreviations: AF = atrial fibrillation; ECG = electrocardiogram; PREVEND = Prevention of Renal and Vascular End-stage Disease; UMCG = University Medical Center Groningen.

Covariate definitions.

Systolic and diastolic blood pressures were calculated as the mean of the last 2 measurements of the 2 visits, using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or use of antihypertensive drugs. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m2), and obesity was defined as a BMI > 30 kg/m^2. Type 2 diabetes was defined as a fasting plasma glucose > 7.0 mmol/L (126 mg/dL), a nonfasting plasma glucose > 11.1 mmol/L, or use of anti-diabetic drugs. Urinary albumin excretion was calculated as the average value from 2 consecutive 24 h urine collections. The estimated glomerular filtration rate (eGFR) was estimated using the simplified modification of diet in renal disease formula. Smoking was defined as current nicotine use or quit smoking within the previous 5 years. Hypercholesterolemia was defined as total serum cholesterol > 6.5 mmol/L (251 mg/dL), or a serum total cholesterol ≥ 5.0 mmol/L (193/mg/dL) if a history of myocardial infarction was present, or use of lipid-lowering drugs. Alcohol consumption was defined as 4 alcoholic drinks per day or more in men, and 1-3 alcoholic drinks per day or more in women. History of myocardial infarction or stroke was defined as participant-reported hospitalization for at least 3 days as a result of this condition. Peripheral artery disease was defined as an ankle-brachial index < 0.9. A committee of heart failure experts adjudicated all participants with heart failure at baseline according to previously published criteria (14). N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and highly sensitive C-reactive protein (high sensitive CRP) were measured as described previously (15,16).

Follow-up.

The follow-up duration was calculated as the time between the baseline-screening visit to the last contact date, death, or December 31, 2008 (end of the third PREVEND follow-up visit), whichever came first.

Cardiovascular events, heart failure and all cause mortality assessment.

Information on cardiovascular events was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. The validity of this database has been confirmed before, with 84% of primary diagnoses and 87% of secondary diagnoses matching the diagnoses recorded in participants' charts (17). Use of hospital discharge diagnoses and government vital statistics was part of the original study design (18). Data were coded according to the 10th revision of the International Classification of Diseases (ICD). Cardiovascular events consisted of cardiac events (acute myocardial infarction [ICD code 410], acute and subacute ischemic heart disease [ICD 411], coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), cerebrovascular events (occlusion or stenosis of the precerebral (ICD 433) or cerebral arteries (ICD 434), subarachnoid

hemorrhage [ICD 430]), and peripheral events (other vascular interventions such as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels). A committee of heart failure experts adjudicated all incident heart failure events according to previously published criteria, and categorized, based on the left ventricular ejection fraction (LVEF) and diastolic dysfunction, into either heart failure with reduced ejection fraction (LVEF < 40%) and heart failure with preserved ejection fraction (LVEF > 50%) (2). Six heart failure participants had a LVEF of 41–49%. These were included in the total number of heart failure patients, but were not involved in analyses specific for this group because of the low number of events. There was no classification made based on underlying cause, since many heart failure patients have more than one comorbidity. Data on mortality were obtained through the municipal registration. Cause of mortality was ascertained by linking the number of the mortality certificate to the primary cause of mortality as coded by the Dutch Central Bureau of Statistics. Information on dates and causes of death for every participant was obtained from Statistics Netherlands (19), according to the 10th revision of the ICD.

Statistical analysis.

We used a statistical weighting method to adjust for the oversampling of individuals with microalbuminuria at study start, and to allow generalization of results to the general population (16). Participant characteristics were presented as mean ± standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. Incidence rates for the number of AF cases or outcome events/1,000 person-years of observation and 95% confidence intervals were calculated (20). We estimated multivariable Cox proportional-hazards regression models to assess risk factors for incident AF during follow-up; death was considered a censoring event. We examined the proportionality assumption by calculating the Schoenfeld residuals, and by plotting the scaled Schoenfeld residuals against time. There were no violations of the proportional-hazards assumption. We selected risk factors for the incident AF analyses based on prior reports and availability in clinical practice (11,12). Age- and sex-adjusted covariates with a $p < 0.1$ were stepwise incorporated in a multivariable-adjusted model, the order based on the highest Wald statistic. The final multivariable model included all covariates with $p < 0.05$. Finally, interactions in the multivariate model were tested. In view of multiple testing, we applied a Bonferroni correction to the interaction analysis, in order to minimize false-positive findings. Population attributable risks for reversible or treatable risk factors in the multivariate model were calculated using the formula: ([total AF incidence rate – unexposed AF incidence rate]/[total AF incidence rate]) x 100% (21). We used Cox time-dependent regression analyses, with AF as time-varying covariate to study the association of incident AF and future cardiovascular events, heart failure and all cause mortality. We adjusted for clinically significant covariates, based on prior

publications (22-24). In Model 1 we adjusted for age and sex, and in Model 2 we adjusted for age, sex, heart failure, antihypertensive drug use, diabetes, previous stroke, previous myocardial infarction, peripheral artery disease, and NT-proBNP. All analyses were performed using R package (version 3.0.3) and a 2-tailed p-value < 0.05 was considered statistically significant.

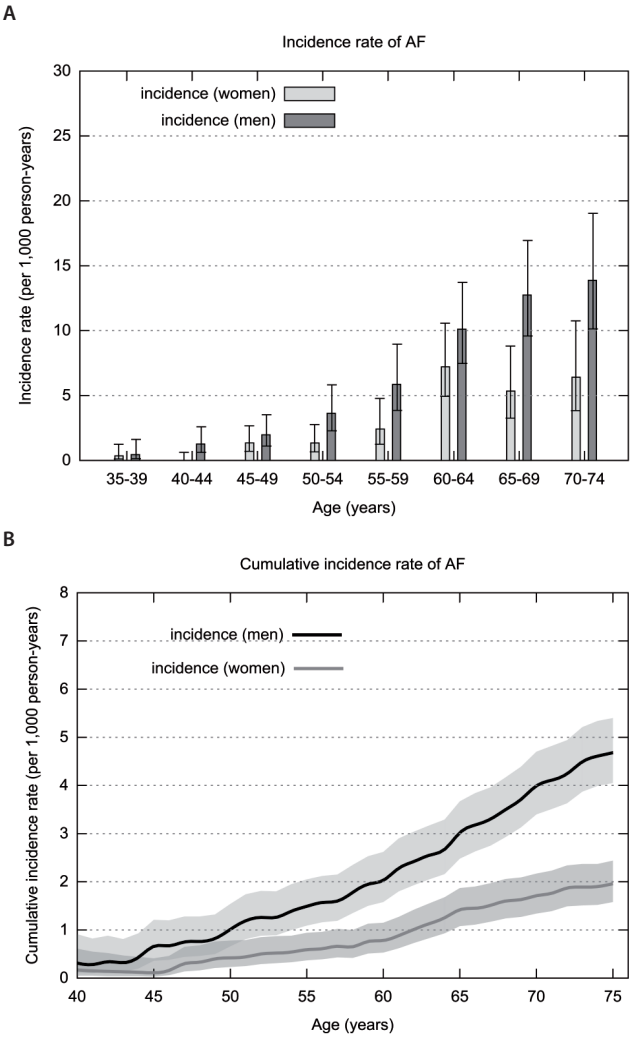


Figure 2. Atrial fibrillation incidence in PREVEND study.
A: Incidence rate of atrial fibrillation as a function of age for men and women. The 95% confidence intervals are shown using error bars. **B:** Cumulative incidence rate of AF as a function of age for men and women. The black line is the (smoothed) cumulative incidence rate curve for men; the grey line for women. The 95% confidence intervals are shown using shaded areas. The cumulative incidence rate at a given age is the incidence rate of atrial fibrillation in the group of all people younger than the given age. Incidence rates are per 1000 person-years of follow-up.
Abbreviations: PREVEND = Prevention of Renal and Vascular End-stage Disease.

RESULTS

Participant characteristics.

Mean age of PREVEND participants was 49 ± 13 years, and 49.8% were men. Total follow-up duration of 8,265 PREVEND participants was 80,352 person-years. During a mean follow-up of 9.7 ± 2.3 years, 265 (80 women, 185 men) participants (3%) developed AF (AF incidence rate 3.3 [95% confidence interval 3.0-3.8] per 1,000 person years; **Table 1**). Participants with incident AF were 62 ± 9 years of age and 70% were men. Of the 265 participants with incident AF, 60 (23%) were diagnosed at a PREVEND visit, the other 205 (77%) at hospital visit or admission. Both cumulative and non-cumulative incidence rates for incident AF stratified by age and sex demonstrated higher AF incidence rates in

Table 1. Participant Characteristics.

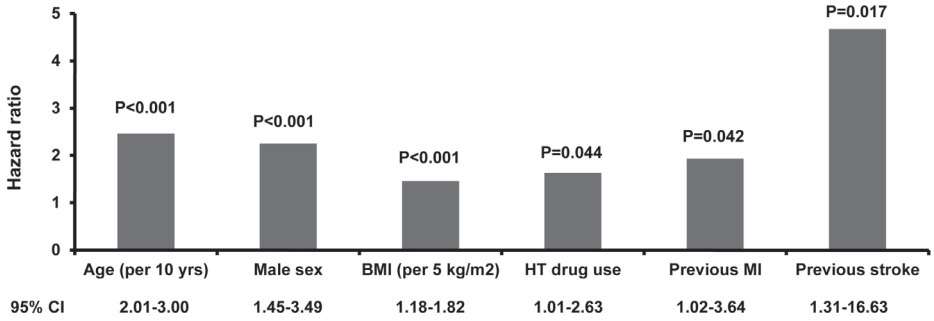
Characteristic	Incident AF (n = 265)	No AF(n = 8,000)	P-value
Age (years)	62 ± 9	49 ± 13	< 0.001
Male sex	185 (70%)	3,935 (49%)	< 0.001
Caucasian	252 (95%)	7,592 (95%)	1.000
BMI (kg/m^2)	28 ± 4	26 ± 4	< 0.001
Obesity	61 (23%)	1,226 (15%)	0.001
Systolic blood pressure (mmHg)	143 ± 23	129 ± 20	< 0.001
Diastolic blood pressure (mmHg)	78 ± 10	74 ± 10	< 0.001
Heart rate (bpm)	67 ± 11	69 ± 10	0.002
Antihypertensive drug use	99 (37%)	999 (12%)	< 0.001
Hypertension	145 (54%)	2,092 (26%)	< 0.001
Previous myocardial infarction	41 (15%)	210 (3%)	< 0.001
Heart failure	6 (2.3%)	12 (0.2%)	< 0.001
Diabetes mellitus	23 (9%)	287 (4%)	< 0.001
Previous stroke	7 (2.6%)	50 (0.6%)	0.002
Peripheral artery disease	28 (11%)	263 (3%)	< 0.001
Smoking	97 (37%)	3,573 (45%)	0.012
Alcohol consumption	31 (12%)	1,023 (13%)	0.641
Hypercholesterolemia	35 (13%)	326 (4%)	< 0.001
PR-interval duration (ms)	168 (153-187)	158 (143-172)	< 0.001
eGFR (ml/min)	75 (68-84)	80 (72-90)	< 0.001
UAE (mg/24h)	16 (8-39)	9 (6-17)	< 0.001
NT-proBNP (ng/L)	103 (44-248)	36 (16-70)	< 0.001
High sensitive CRP(mg/L)	2.0 (0.8-3.6)	1.3 (0.6-2.9)	< 0.001

Data is expressed as mean±standard deviation (SD), median (IQR) or numbers (%).
Abbreviations: BMI = body mass index; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; UAE = 24-hour urine albumin excretion.

older individuals (**Figure 2A and B**). Primary comorbidities in participants with incident AF were hypertension (54%), obesity (23%), and previous myocardial infarction (15%).

Risk factors for incident AF.

Age- and sex-adjusted analyses revealed that higher BMI, higher systolic blood pressure, antihypertensive drug use, previous myocardial infarction, heart failure, previous stroke, lower heart rate, and higher NT-proBNP were associated with an increased risk of incident AF (**Table 2**). After stepwise addition of covariates, the final multivariable model consisted of 6 covariates (**Central Illustration**): advancing age, male sex, BMI, antihypertensive drug use, previous myocardial infarction, previous stroke. There were no significant interactions in the multivariate model. Population attributable risk estimates for the most significant reversible or treatable risk factors for incident AF were calculated: The risk factor that contributed most to incident AF in the present population was antihypertensive drug use (32%), followed by previous myocardial infarction (16%), obesity (9%) and previous stroke (3%).



Central Illustration. AF in community-based cohort in the Netherlands: Multivariate determinants of incident AF.

Bars represent the hazard ratio for each individual risk factor for incident atrial fibrillation in the multivariate model. The 95% confidence intervals are shown under each bar.

Abbreviations: AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; HT drug use = antihypertensive drug use; MI = myocardial infarction.

Associations of AF with cardiovascular events, heart failure and all cause mortality.

Incidence rates of cardiovascular outcomes for participants with and without incident AF are described in **Table 3.** Incidence of cardiovascular events in participants with AF was higher compared to participants without AF (incidence rate per 1,000 person years = 20.59 [95% CI 14.84-28.64] vs. 10.13 [95% CI 9.43-10.87] respectively; HR 1.97 [95% CI 1.24-3.13]). Cardiac events were most common, followed by cerebrovascular and peripheral events. The incidence rate per 1,000 person years of heart failure after diagnosis of AF was 18.14 (95% CI 13.19-25.01), compared to 2.91 (95% CI 2.55-3.31) in

Table 2. Age and Sex-adjusted Cox Proportional Hazards Models for Determinants of Incident AF.

Covariate	Hazard Ratio (95% Confidence Interval)	P-value
BMI (per 5 kg/m2)	1.45 (1.21-1.74)	< 0.001
Systolic blood pressure (per 10 mmHg)	1.11 (1.01-1.22)	0.025
Heart rate (per 5 bpm)	0.89 (0.81-0.98)	0.022
Antihypertensive drug use	2.14 (1.43-3.20)	< 0.001
Previous myocardial Infarction	2.56 (1.51-4.35)	< 0.001
Heart failure	2.72 (1.06-6.97)	0.037
Previous stroke	4.63(1.50-14.26)	0.008
NT-proBNP (per 1,000 ng/L)	1.08 (1.07-1.10)	< 0.001

Abbreviations: BMI = body mass index; NT-proBNP =N-terminal prohormone of brain natriuretic peptide.

Table 3. Incidence Rates of Cardiovascular Events, Heart Failure and All Cause Mortality per 1000 Person Years.

	Incidence Rate per 1000 Person Years (95% Confidence Interval)		Hazard ratio (95% Confidence Interval)
	Incident AF (n = 265)	No AF(n = 8,000)	
Cardiovascular events*	20.59 (14.84-28.64)	10.13 (9.43-10.87)	1.97 (1.24-3.13)
Cerebrovascular events	5.53 (3.26-9.46)	2.42 (2.10-2.79)	2.23 (0.99-5.00)
Cardiac events	14.58 (10.05-21.21)	7.54 (6.95-8.19)	1.88 (1.12-3.16)
Peripheral events	1.63 (0.66-4.17)	0.72 (0.56-0.94)	2.20 (0.52-9.37)
Heart failure	18.14 (13.19-25.01)	2.91 (2.55-3.31)	6.01 (2.83-12.76)
LVEF < 40%	12.75 (8.72-18.68)	1.99 (1.70-2.33)	5.79 (2.40-13.98)
LVEF > 50%†	4.90 (2.69-9.02)	0.85 (0.67-1.08)	4.80 (1.30-17.70)
All-cause mortality	28.96 (23.05-36.42)	6.84 (6.28-7.44)	4.14 (2.64-6.51)

*Composite of cardiovascular events, some participants had multiple events.
†Six heart failure participants had a LVEF of 41–49%. To ensure a clear distinction between both systolic and diastolic heart failure these participants were not shown in the table.
Abbreviations: LVEF = left ventricular ejection fraction.

participants without AF (HR 6.01 [95% CI 2.83-12.76]). Heart failure with reduced ejection fraction was more common than heart failure with preserved ejection fraction. The incidence rate per 1,000 person years of all cause mortality after diagnosis of AF was 28.96 (95% CI 23.05-36.42), compared to 6.84 (95% CI 6.28-7.44) in participants without AF (HR 4.14 [95% CI 2.64-6.51]). Incident AF was associated with cardiovascular events (multi-variable adjusted HR 2.24 [95% CI 1.06-4.75], p = 0.035), with heart failure (multi-variable adjusted HR 4.52 [95% CI 2.02-10.09], p < 0.001), and with all cause mortality (multi-variable adjusted HR 3.02 [95% CI 1.73-5.27], p < 0.001) (**Table 4**). Incident AF was associated with both heart failure with reduced ejection fraction (multi-variable adjusted HR 4.00 [1.49-10.73], p = 0.006) and preserved ejection fraction (multi-variable adjusted HR 6.82 [2.47-18.79], p < 0.001).

Table 4. Association of Incident AF* with Outcomes.

	Hazard ratio (95% Confidence Interval)	P-value
Cardiovascular events		
Model 1	2.45 (1.34-4.49)	0.004
Model 2	2.24 (1.06-4.75)	0.035
Heart failure		
Model 1	6.11 (3.32-11.23)	< 0.001
Model 2	4.52 (2.02-10.09)	< 0.001
All cause mortality		
Model 1	3.79 (2.34-6.14)	< 0.001
Model 2	3.02 (1.73-5.27)	< 0.001

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, prevalent heart failure, antihypertensive drug use, diabetes, previous stroke, previous myocardial infarction, peripheral artery disease, N-terminal prohormone of brain natriuretic peptide.
*Time-varying covariate.

DISCUSSION

The present contemporary community-based study in the Netherlands had 3 primary findings. First, the AF incidence in the present population was 3.3 per 1,000 person years, and comparable to that in older epidemiological studies. Second, in addition to the conventional risk factors for AF, BMI was strongly associated with AF. Third, we confirmed that AF, despite lower overall event rates, is associated with an adverse outcome.

Incidence of AF.

In the present study, we identified 265 participants with incident AF, and the overall incidence rate of AF was 3.3 per 1,000 person years. AF incidence was higher in men than in women, and there was a strong increase with age, which is comparable to other studies (5-8,25). The incidence is lower than observed in the Rotterdam Study, also from the Netherlands, where the overall incidence rate of AF was 9.9 per 1,000 person years. This is probably caused by the age difference of included individuals (in Rotterdam > 55 years, in PREVEND between 28 and 75 years) (25). Many of the epidemiological studies on AF--i.e. Olmsted County (AF documented 1980-2000) (8), the Cardiovascular Health Study (inclusion from 1989-1993, last evaluation for AF 1996) (6), Atherosclerosis Risk in Communities (inclusion 1987-1989, follow-up until 1998) (7), and the Rotterdam Study (inclusion 1990-1993, follow-up until 1999) (25)--followed their participants up to the 21st century, except the Framingham Heart Study (inclusion 1948-1971, follow up until 2008) (4,5), and the Women's Health Initiative (inclusion 1994-1998, follow-up until 2007) (21). Our AF incidence rate is comparable to the incidences described in those older, and predominantly U.S.-based cohort studies (range 3.3-19.2 per 1,000 person years)

(5-8,25). This is an interesting finding, because continuously improvements are made in the treatment of cardiovascular risk factors for AF including hypertension, coronary heart disease, and heart failure (11-13). Whereas improved treatment of cardiovascular diseases may reduce the risk of development of AF, on the contrary, the improved life expectancy, changes in lifestyle such as inactivity and obesity, may increase the incidence of AF. Together, this may have resulted in an AF incidence in the present study being comparable to older studies.

Comorbidities associated with incident AF.

Most data on comorbidities associated with AF in the general population have been obtained from old American cohorts starting their inclusion before the introduction of contemporary treatments for myocardial infarction, hypertension and heart failure, and increasing availability of diagnostic tests, and changing lifestyle (11-13,26).

Associations of advancing age, male sex, hypertension, coronary heart disease, valve disease, heart failure and diabetes mellitus with incident AF have been well established (4,6,7,21,25). In the present contemporary Dutch cohort we found similar associations of well-established risk factors. In addition, obesity was an important contributor to AF risk. In a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference published in 2011 (12), BMI was considered a less-validated risk factor for AF. However, with a 45% increased risk of AF with every 5 points of BMI increase, the present study supports the notion that BMI should be regarded as a validated risk factor for AF.

Obesity often co-exists with other cardiovascular risk factors and diseases,e.g. diabetes, metabolic syndrome, and the sleep apnea syndrome. However, obesity by itself may also induce AF. Animal models of obesity showed the induction of cardiac ectopic fat and fat infiltration of the local atrial myocardium, potentially a novel substrate specific to obesity (3). Importantly, obesity is a modifiable risk factor, and it has been recently shown that strict weight reduction reduced the AF burden (29). The population attributable risk of obesity in this study provides an indication that 9% reduction of incident AF could be achieved when the risk factor obesity was completely eliminated.

AF related cardiovascular events, heart failure and mortality.

The present analysis confirms the association of AF with adverse outcomes, including cardiovascular events, heart failure and all cause mortality. Treatment of AF has significantly changed during the last decade. The most important change has been systematic use of oral anticoagulation in individuals at risk for stroke (4). While the overall event rates were lower in the present contemporary cohort, the associations with outcome were similar as previously described. The lower rates of cardiovascular events, heart failure and all cause mortality may be caused by improved treatment modalities. However,

incident AF was still associated with a 2-fold increase of cardiovascular events including stroke, a 5-fold increased heart failure risk, and a 2-fold increased risk of all cause mortality, largely similar to associations found previously (23,24). Despite the important improvements in oral anticoagulation reducing the risk of stroke (30-32), the risk of heart failure and all cause mortality associated with AF are still high (24). Next to stroke prevention, more focus on prevention of heart failure and mortality in individuals with AF seems important in the years to come, to further improve prognosis of those with AF.

Strengths and limitations.

Strengths of our study are the contemporary cohort, the detailed clinical assessment, the long and contemporary follow-up period, and the robust validation of cardiovascular events, including AF. However, there are limitations, mainly due to the observational design of this community-based cohort study. We may have overlooked asymptomatic paroxysmal AF, since we had no continuous ECG recordings (33). And since an event was only attributed to AF when AF was diagnosed before the event occurred, the present event rates may be underestimated. Stroke was defined using ICD codes for occlusion or stenosis of the precerebral or cerebral arteries; no direct evaluation for stroke was performed. Data on obstructive sleep apnea was not available. Although treating physicians were informed about presence of AF or other undiagnosed cardiovascular diseases, treatment was left to discretion of the physician.

CONCLUSIONS

Results of our contemporary community-based study from the Netherlands confirm that although important progress in treatment of cardiovascular disease is continuously being made, AF incidence has not dramatically changed over the years. Obesity has become a major risk factor for incident AF. While overall event rates were lower in the present study, incident AF still doubles the cardiovascular event risk, all cause mortality risk and increases the heart failure risk 5-fold. Identification and improved treatment of reversible risk factors for incident AF, and prevention of heart failure and mortality, may avoid AF and improve AF prognosis.

PERSPECTIVES

Competency in Medical Knowledge.

Despite considerable progress in management of cardiovascular disease, the incidence of AF has not decreased and this common rhythm disturbance is associated with ad-

verse cardiovascular outcomes, including heart failure and stroke. In addition to well-established factors, obesity has become a risk factor for AF.

Translational Outlook.

More research should be directed toward understanding the roles of weight reduction and lifestyle modification in prevention of AF.

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Chapter 3

Does myocardial infarction beget atrial fibrillation and atrial fibrillation beget myocardial infarction?

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INTRODUCTION

Atrial fibrillation (AF) affects millions of people worldwide.(1) It is already known several decades that AF is not a benign condition, and it's associated with a 5-fold increased risk of stroke, 3-fold increased risk of heart failure, and doubling of risk of dementia and death.(2-4) Myocardial infarction, and coronary heart disease, are traditional risk factors of AF,(5) however, whether myocardial infarction is a consequence of AF, has not been studied in great detail yet. The focus of current treatment for AF is pointed towards prevention of stroke. This is of utmost importance; however the other cardiovascular morbidities and mortality should not be overseen. An analysis of patients originally diagnosed with idiopathic AF, demonstrated that these patients develop frequently cardiovascular disease, including myocardial infarction and coronary artery disease.(6) An analysis of Medicare data emphasized the importance of cardiovascular events beyond stroke, such as heart failure, myocardial infarction and death in older adults with AF.(7)

In the current issue of *Circulation*, Soliman et al. describe the association of AF with myocardial infarction.(8) Similar findings in 2 other cohorts by the same lead author have been published in the last months.(9,10) First, the analysis of 23,928 US residents without coronary heart disease included in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort demonstrated that prevalent AF was associated with a 2-fold higher incidence of myocardial infarction.(9) Risk of myocardial infarction was significantly higher in women and blacks. Second, the analysis from the Cardiovascular Health Study (CHS) showed similar associations.(10) Third, in current issue of *Circulation*,(8) Soliman and colleagues present an analysis of 14,462 participants who were free of coronary heart disease at baseline, included in the Atherosclerosis Risk in Communities (ARIC) study. The authors investigated the association of AF as a time-varying variable (n=1545) with overall incident myocardial infarction, and by type of myocardial infarction (ST elevation myocardial infarction [STEMI] or non-ST elevation myocardial infarction [NSTEMI]). Atrial fibrillation was associated with a 63% increase in risk of myocardial infarction after multivariable adjustments. The association was limited to NSTEMI; no association with STEMI was found. In accordance with REGARDS, women had higher risks of developing myocardial infarction, than men. Racial differences did not reach statistical significance here.

How can we explain the recent findings in several independent cohorts? Is it because the prevalence of both AF and myocardial infarction are increasing, and is it a matter of time until both conditions happen in the same individual? Or is it because the high-sensitive troponin assays enhance the detection of minimal myocardial damage, and the diagnosis of myocardial infarction, especially NSTEMI, is made more often than in

the old days, and may even represent myocardial damage as result of AF itself rather than result of atherosclerosis?(11) However, there are also other possible explanations.

Firstly, both AF and myocardial infarction share many cardiovascular risk factors including age, hypertension and diabetes mellitus.(12) Possibly the association of AF and myocardial infarction reflects a final common pathway of underlying vascular disease. Extrapolating ideas from the relation of AF and stroke to the relation of AF and myocardial infarction may be of value to support this notion. There has always been a strong belief that AF, clot formation and stroke are temporally linked, especially since this fits Virchov's trias with low flow, increased plasma clotting factors and vessel wall, i.e. atrial wall abnormalities. However, the ASymptomatic AF and Stroke Evaluation in pacemaker patients and the AF Reduction atrial pacing (ASSERT) Trial has recently shown that there is a temporal disconnect between stroke and continuously monitored occurrence of AF.(13) This suggests that stroke, and probably also myocardial infarction, and AF have pathophysiological mechanisms in common. This is also reflected by the CHA_2DS_2-VASc score, the risk of stroke depends on the number of cardiovascular conditions present in patients with a diagnosis of AF, and not on the number of AF recurrences after the initial diagnosis.(2,3) However, the explanation of shared risk factors, and common pathways, negates the complex relations between AF and myocardial infarction. Myocardial infarction, and transient ischemia, may beget AF.(14) Myocardial infarction, and coronary heart disease, are well-established risk factors for incident AF,(12) and subclinical coronary artery disease also increases AF risk, potentially via atrial remodeling or transient ventricular ischemia with atrial diastolic overload.(5,15) Studies investigating oral anticoagulants in AF suggested an increased risk of myocardial infarction in patients with AF,(16,17) and it has been suggested that there are differences between the diverse oral anticoagulants in reducing risk of myocardial infarction.(18,19) The opposite, AF may beget myocardial infarction also seems true, as was convincingly demonstrated by the studies authored by Soliman.(8-10) Atrial fibrillation may lead to myocardial infarction through increased heart rate and thus increased oxygen demand, sympathetic activation, endothelial dysfunction, and pro-inflammatory and pro-thrombotic effects (**Figure 1**).(14) The finding that NSTEMI, but not STEMI was associated with AF, supports the notion that recurrent ischemia is more frequently associated with NSTEMI compared to STEMI. However, coronary angiograms, which might substantiate this, were not routinely done in present community-based studies.(8-10) Also, coronary stenosis or occlusion on coronary angiograms or performed percutaneous coronary interventions were not essential for the diagnosis of myocardial infarction in these cohorts.

The authors are congratulated for their contribution to the literature. Their findings once again underscore the need for a detailed search for underlying causes and risk factors of AF, and also strict follow up to determine risk of cardiovascular events, beyond stroke.

Previously, strict implementation of AF guidelines using nurse-led care has shown to improve overall AF-related outcomes, including cardiovascular events beyond stroke. (20) Currently, the IntegRAted CarE for Atrial Fibrillation (RACE-4) study, a randomized multicenter study in the Netherlands, is recruiting up to 1716 patients to further study whether strict evaluation and follow-up of individuals with AF by specialized nurses can improve AF-related outcomes. It is also a call for more research to better understand the causality of both conditions, and the underlying pathophysiology. This cannot be established from present community-based cohort studies.

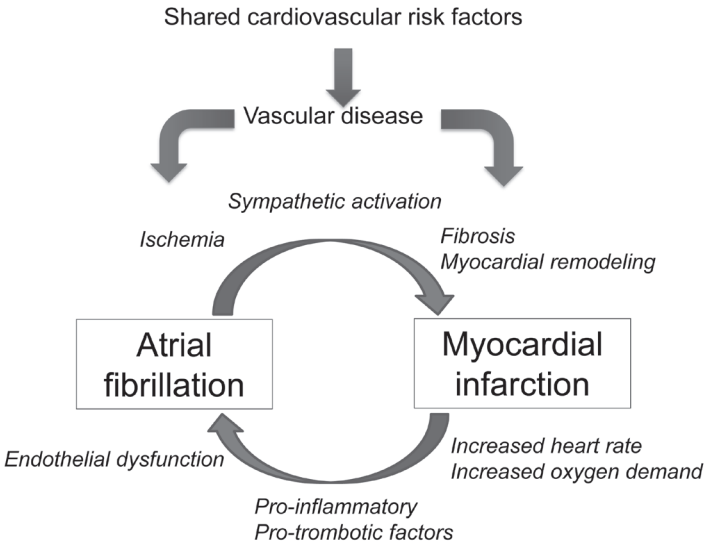

Figure 1. Conceptual figure of the bidirectional relation between atrial fibrillation and myocardial infarction.

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Chapter 4

Clinical profiles in atrial fibrillation depend on age of onset

Manuscript submitted.

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ABSTRACT

Background.

Atrial fibrillation (AF) is mostly observed in patients at older age in the presence of underlying diseases. However, nowadays clinicians frequently encounter patients with AF onset at young age.

Objectives.

We studied differences in clinical profile according to age of AF onset.

Methods.

We performed a prospective, single-center, observational study. Consecutive patients, age < 60 years ('young AF patients'), with short-lasting AF (<3 years) were compared with AF patients with AF onset ≥ 60 years ('older AF patients'), and with age- and sex-matched controls (< 60 years).

Results.

Median age at AF onset was 51 (interquartile range [IQR] 44-54) in young and 66 [IQR 63-70] years in older patients. Young AF patients were more often men (70% vs. 56%, p=0.02), had less hypertension (41% vs. 63%, p<0.001), lower NT-proBNP plasma levels in sinus rhythm (83 [IQR 26-119] vs. 159 [IQR 83-298] ng/l, p<0.001), less left ventricular hypertrophy or remodeling (20% vs. 40%, p<0.001), better diastolic function, less atrial dilatation (39% vs. 55%, p=0.04), and better left atrial reservoir and conduit function. Obesity was prevalent both in young (34%) and older (28%) patients. Younger patients more frequently had familial AF (28% vs. 12%, p<0.001) and cardiomyopathies (7% vs. 0%, p=0.007). Lone AF was rare in both groups, 2% vs. 0%, respectively, p=0.25.

Conclusions.

Distinguishable clinical profiles exist according to age of AF onset. Younger patients were more often men with familial AF, who less frequently suffered from hypertension and diastolic dysfunction. Even in young patients, lone AF was very rare.

INTRODUCTION

Atrial fibrillation (AF) often occurs at advanced age, and most commonly in the presence of concomitant cardiovascular disease, such as heart failure, hypertension, coronary heart disease and diabetes.(1-4) Yet, clinicians frequently encounter younger patients (<60 years) with AF.(4-6)

In epidemiological studies AF incidence in young individuals (aged 20-60 years) ranges between 0.17-3.8 per 1000 person years, and AF prevalence from 0.03-1.46%.(4, 7) However, the incidence of AF in young patients increases.(7) This seems associated with changes in life style, consumption pattern and lack of exercise, which may lead to earlier development of cardiovascular risk factors and conditions.(7-9) Also risk factors for AF may differ between young and older individuals.(10) The relative contribution of heritability, as well as contribution of life style-related risk factors such as obesity, and lack of or intensive physical exercise may be greater in young individuals.(3) Yet, data on the exact clinical phenotype of young onset AF is sparse, since almost all data on clinical risk factors for AF are based on older AF patients.(9)

The general notion often is that many young AF patients have lone AF, i.e. AF occurring in the absence of AF risk factors. However recent work suggests that lone AF is present only in a minority, and that even in young patients AF often is accompanied with significant comorbidities.(11)

In the present prospective, single-center, observational study we aim to compare the clinical risk profile of patients with AF onset <60 years to AF patients aged ≥60 years, as well as age- and sex-matched controls.

METHODS

Study population.

The Phenotyping Young-Onset Atrial Fibrillation Patients study is a single-center, prospective, observational study. The institutional review board approved the study protocol. All patients gave written informed consent. Consecutive patients with AF at an age <60 years, who were at least 18 years of age and provided written informed consent were included. Excluded were patients with post-operative AF, myocardial infarction or acute coronary syndrome < 1 month before start of AF, AF due to an acute trigger (e.g. sepsis), and patients with hyperthyroidism < 3 month before start of AF. Baseline assessment included a detailed medical history including family history, physical examination, 12-lead electrocardiogram (ECG), collection of information on underlying disease, conventional and life style-related risk factors for AF, as well as blood samples for biomarker analyses. For evaluation of NT-proBNP plasma levels, distinction was made between

patients in AF and sinus rhythm at the time of blood collection.(12) Between August 2012 and December 2013, 500 patients were included in the University Medical Center Groningen, The Netherlands. In the present analysis consecutive patients with short-lasting AF <3 years without prior pulmonary vein isolation (n=120) were compared to 120 consecutive short lasting (<3 years) AF patients with AF onset ≥60 years who were prospectively included in the AF Risk Profile study (clinicaltrials.gov ID: NCT01510210; prior pulmonary vein isolation is an exclusion criterion). In addition, comparisons were made with age- and sex-matched controls without AF from Prevention of Renal and Vascular Endstage Disease study, a community-based study from Groningen, The Netherlands.(7)

Echocardiography.

At baseline patients underwent a standard two-dimensional transthoracic echocardiogram (General Electric Vivid E9) during continuous ECG monitoring. Left atrial volume was measured using the biplane Simpson's method. Left ventricular mass and relative wall thickness was calculated according to current recommendations to assess left ventricular geometry.(13) In addition, total atrial conduction time (14) and left atrial strain measurements were performed.(15) Measurements were indexed for body surface area where appropriate. Atrial strain measurements (%) representing atrial reservoir function and atrial contraction were measured using two-dimensional speckle tracking. A lower peak strain value corresponds to less compliant atria walls and an impairment of reservoir function.(16) Atrial strain representing conduit function was calculated as the difference between strain during atrial reservoir function and atrial contraction. Only diastolic function and atrial strain measures collected during sinus rhythm were included in the present analysis.

ECG traits suggestive of (subclinical) cardiomyopathies.

ECGs of AF patients during atrial fibrillation and sinus rhythm were adjudicated for traits suggestive of (subclinical) cardiomyopathies by two investigators (RAV and ICVG), with only access to age, sex and medication use.(17)

Definitions.

Hypertension was defined as systolic blood pressure >140mmHg and diastolic blood pressure >90mmHg or by use of antihypertensive medication. Diabetes mellitus was defined as use of anti-diabetic drugs. Patients were classified as having heart failure in the presence of a LVEF≤ 45% ('reduced ejection fraction') at baseline or LVEF> 45% ('preserved ejection fraction') with symptoms associated with heart failure (New York Heart Association functional class II or III) or previous hospitalization for heart failure. Coronary heart disease was defined as a history of myocardial infarction, percutaneous

coronary intervention or coronary artery bypass graft. Peripheral artery disease was defined on the basis of a clinical diagnosis by a vascular specialist or observed with doppler ultrasonography or other imaging technique. The ratio of weight to height squared (kg/m^2) was used for calculation of body mass index (BMI). Obesity was defined as BMI >30 kg/m^2. High alcohol use was defined as ≥8 units per week. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. History of intensive exercise was defined as present or past professional or intensive sports practice. Familial AF was defined as a history of AF before age of 60 years in one or more first-degree family members. Inflammatory disease includes rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease, multiple sclerosis, sarcoidosis (no evidence of cardiac involvement), M. Sjögren, psoriasis. Left ventricular (LV) hypertrophy or remodeling was classified using left ventricular mass index (LVMI) >95 g/m^2(women) or >115 g/m^2(men) and/or relative wall thickness (RWT) >0.42.(13) Concentric remodeling: LVMI ≤95 g/m^2(women) or ≤115 g/m^2(men) and RWT>0.42. Concentric left ventricular hypertrophy: LVMI >95 g/m^2(women) or >115 g/m^2(men) and RWT >0.42. Eccentric left ventricular hypertrophy: LVMI >95 g/m^2(women) or >115 g/m^2(men) and RWT ≤0.42. Diastolic dysfunction was defined as left atrial volume index (LAVI) ≥34 ml/m^2 or e' sept <8 cm/s or e' lat <10 cm/s.(18) Lone AF was defined as absence of any aforementioned risk factors or comorbidities, as well as moderate or severe valve disease, cardiomyopathy, prior stroke, deep vein thrombosis or pulmonary embolism, high alcohol use, current smoking, BMI >25, low voltage ECG, ST elevation in V1-2, ventricular rate <120bpm during AF without rate control drugs which is suggestive of intrinsic cardiac disease, and eGFR <60.

Statistical analysis.

Descriptive statistics are presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables, and numbers with percentages for categorical variables. We evaluated differences between young-onset AF patients, older AF patients and age- and sex-matched controls at baseline using the chi-square test and Fisher exact test for categorical data, and the T-test and Mann-Whitney-U test for continuous data, depending on the normality of the data. In secondary analyses, comparisons were made between young women and men, and between young women or men with older women or men, respectively. When sex-related differences were observed between younger and older patients, logistic or linear regression analysis was used to evaluate interactions of age (stratified for age <60years and >60years) and sex for these possible differences. If appropriate, log transformations were performed to provide normal distribution of residuals in linear regression. In addition we studied the subset of patients who developed AF at a very young age (<40 years, n=19). A chi-square test for linear trend was used to examine relations of risk factors with the three age groups <40years, 40-60 years and >60years. In all analyses a value of $p<0.05$ was considered statistically significant.

RESULTS

Differences in clinical risk factors between young and older AF patients.

In young patients, median age of AF onset was 51 (IQR 44-54) years (**Table 1**). AF temporal patterns were not different between young and older patients. Young patients were more often men (70% vs. 56%, p=0.02), had less hypertension, and lower plasma NT-proBNP plasma levels (collected in sinus rhythm). Obesity was highly prevalent in both young and older patients (34% vs. 28%, p=0.37). Lone AF was rare in both groups (2% vs. 0%, p=0.25). Young patients more often performed regular physical activity (≥3 times per week) for longer periods of time (>60minutes). Younger patients more often had familial AF (28% vs. 12%, p<0.001) and cardiomyopathies (7% vs. 0%, p=0.007). The **Central Figure** shows the relative importance of AF risk factors in both AF groups.

Sex related differences in clinical risk factors.

Prevalence of hypertension, coronary heart disease, other traditional risk factors, BMI and obesity were comparable between young men (n=84) and young women (n=36). However young men more often had high alcohol intake (26% vs. 11%, p=0.03) and lower NT-proBNP plasma levels (68 [IQR 24-108] vs. 97 [IQR 69-235] ng/l, p=0.02) than young women. **Supplementary Table 1** shows differences between young and older men, and young and older women. Calculation of the interaction between age and sex (**Supplementary Table 2)** showed that taller stature in young men compared to older men (but not in women), was the only significant sex-related difference in clinical risk factors (p=0.01 for interaction between age and sex).

Differences in clinical risk factors between young AF patients and age- and sex-matched controls.

Compared to age- and sex-matched controls, young AF patients more often had hypertension (41% vs. 21%, p=0.001), higher weight, higher body mass index and were more often obese (34% vs. 15%, p<0.001). Young patients also had slower heart rates in sinus rhythm and more often had PR-interval >200ms. The prevalence of heart failure, myocardial infarction, diabetes mellitus, and stroke was low in young AF patients, and comparable to controls. Young AF patients had taller stature than controls, although this difference was only found in men when both sexes were analyzed separately (186±8 vs. 178±6 cm, p<0.001 in men; 172±7 vs. 169±7 cm, p=0.17 in women). No other sex-related differences were found between young AF patients and controls.

Table 1. Characteristics of patients with AF onset < 60 years and AF ≥60 years

	AF onset <60yr (n=120)	AF onset ≥60yr (n=120)	P-value
Age AF onset (years)	51 (44-54)	66 (63-70)	<0.001
Total AF history (years)	1.5 (0.7-2.4)	0.5 (0.2-1.1)	<0.001
Men	84 (70)	67 (56)	0.02
Type of AF			0.08
Paroxysmal	86 (72)	91 (76)	
Persistent	29 (24)	29 (24)	
Permanent	5 (4)	-	
AF EHRA class			0.11
I	14 (11)	23 (19)	
II	83 (69)	70 (58)	
III	21 (18)	27 (23)	
IV	2 (2)	-	
Frequency symptoms			0.22
Occasional (<1x/month)	67 (56)	54 (44)	
Intermediate (1x/month to daily)	29 (24)	33 (28)	
Frequent (daily)	24 (20)	33 (28)	
HFrEF	4 (3)	6 (5)	0.75
HFpEF	1 (1)	4 (3)	0.21
Previous admission for heart failure	4 (3)	7 (6)	0.54
Hypertension	49 (41)	76 (63)	<0.001
Diabetes mellitus	9 (8)	18 (15)	0.07
Vascular disease	13(11)	25(21)	0.03
Coronary heart disease	8 (7)	11 (9)	0.47
Peripheral artery disease	-	4 (3)	0.12
Prior stroke	5 (4)	11 (9)	0.12
Moderate or severe valve disease	3 (3)	6 (5)	0.50
Cardiomyopathy	8 (7)	-	0.007
Hypertrophic	5 (4)	-	0.12
Thyroid disease	3 (3)	14 (12)	0.01
Inflammatory disease	4 (3)	9 (8)	0.25
Deep vein thrombosis or pulmonary embolism	3 (3)	4 (3)	1.00
High alcohol use	26 (22)	20 (17)	0.13
Current smoking	19 (16)	16 (13)	0.48
Vagal AF triggers	53 (44)	58 (48)	0.40
Lone AF	2 (2)	-	0.25
CHA_2DS_2-VASc	1 (0-1)	2 (1-3)	<0.001
Total number of comorbidities	1 (0-1)	1 (0-1)	0.002
Familial AF	34 (28)	14 (12)	<0.001

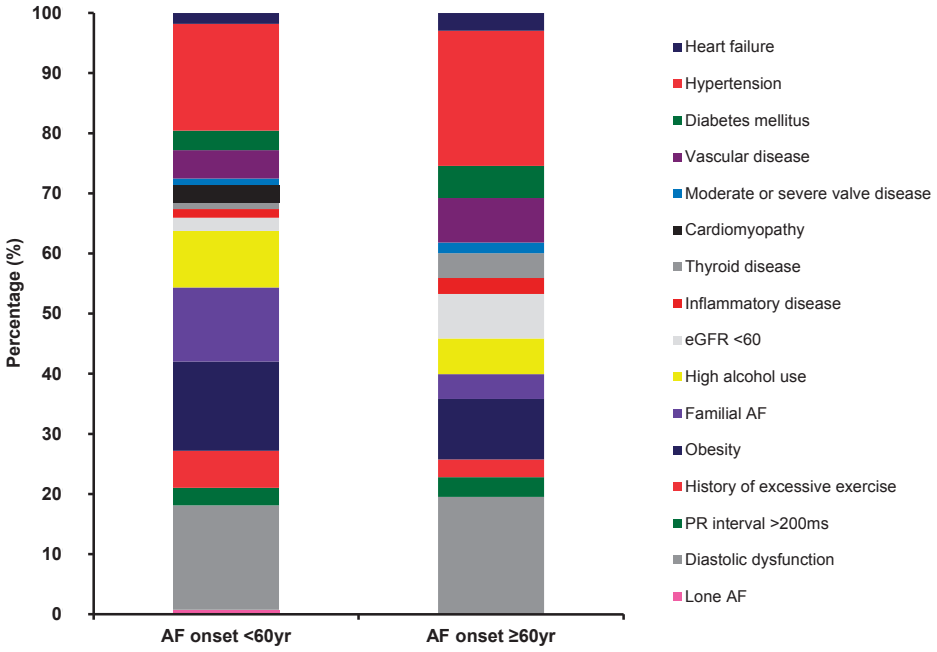
Table 1. Characteristics of patients with AF onset < 60 years and AF ≥60 years (continued)

	AF onset <60yr (n=120)	AF onset ≥60yr (n=120)	P-value
Physical examination			
Height (cm)	182±10	176±8	<0.001
Weight (kg)	94±17	85±14	<0.001
BMI (kg/m^2)	28.4±4.8	27.7±4.5	0.32
Obesity	41 (34)	34 (28)	0.37
Systolic blood pressure (mmHg)	126±19	133±16	0.001
Diastolic blood pressure (mmHg)	80±11	79±9	0.72
Physical activity			
Physical activity ≥3 times per week	37 (31)	24 (20)	0.007
Physical activity >60 min per activity	26 (22)	8 (7)	<0.001
Moderate/high dynamic	37 (31)	34 (28)	0.20
Moderate/high static	24 (20)	14 (12)	0.02
History of intensive exercise	17 (14)	10 (8)	0.18
Electrocardiogram			
Heart rate (bpm, sinus rhythm)	66±11	64±12	0.14
PR interval (ms)	161±26	171±23	0.006
Other ECG abnormalities	13 (11)	6 (5)	0.09
Low voltage ECG	6 (2)	3 (1)	0.50
ST-elevation V1-2	7 (6)	3 (3)	0.33
Echocardiography			
Left atrial parasternal long axis (mm)	39±6	40±6	0.22
Left atrial volume index >34ml/m^2 (%)	39	55	0.04
Right atrial length (mm)	53±6	54±7	0.71
Right atrial width (mm)	41±6	40±7	0.51
LV end-diastolic diameter Index (mm/m^2)	23 (22-25)	24 (22-25)	0.22
LV end-systolic diameter Index (mm/m^2)	15 (13-17)	15 (14-17)	0.18
LV mass index (g/m^2)	79 (68-89)	80 (71-92)	0.24
LV hypertrophy or remodeling	24 (20)	48 (40)	<0.001
Concentric LV remodeling	18 (15)	35 (29)	0.003
Concentric LV hypertrophy	2 (2)	10 (8)	0.02
Eccentric LV hypertrophy	4(3)	3(3)	1.00
LV ejection fraction (%)	58 (55–60)	58 (55-60)	0.26
E' septal (cm/s)	10±3	8±2	<0.001
E' lateral (cm/s)	13±3	9±3	<0.001
E/e'	6 (5-7)	8 (6-10)	<0.001
Diastolic dysfunction (%)	54	88	<0.001
Total atrial conduction time (ms)	130±25	136±25	0.22
LA reservoir function (%)	31±9	26±9	0.003
LA contraction function (%)	12±4	13±5	0.61
LA conduit function (%)	18±7	14±6	<0.001

Table 1. Characteristics of patients with AF onset < 60 years and AF ≥60 years (continued)

	AF onset <60yr (n=120)	AF onset ≥60yr (n=120)	P-value
Laboratory results			
Creatinine (umol/l)	78 (68–86)	78 (71-95)	0.12
eGFR (ml/min*1.73)	87±18	75±17	<0.001
eGFR<60 ml/min	6 (5)	25 (21)	<0.001
Total cholesterol (mmol/l)	5.2 (4.6-6.0)	5.0 (4.1-6.0)	0.26
Glucose (mmol/l)	5.5 (5.1-6.0)	6.0 (5.6-6.8)	<0.001
NT-proBNP during sinus rhythm (ng/l)	83 (26–119) **(n=58)**	159 (83-298) **(n=59)**	<0.001
NT-proBNP atrial fibrillation (ng/l)	383 (144–1291) **(n=36)**	700 (141-1260) **(n=43)**	0.36

Data is expressed as mean±standard deviation(SD), median(IQR) or numbers(%).
Abbreviations: AF=atrial fibrillation; AF EHRA class=European Heart Rhythm Association AF symptom class; BMI=body mass index; bpm=beats per minute; CHA_2DS_2-VASc=stroke risk index (history of heart failure, hypertension, age >65 or >75 years, diabetes mellitus, stroke or vascular disease); ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LA=left atrium; LV=left ventricle; LVMI=left ventricular mass index(g/m^2); NT-proBNP=N-terminal prohormone of brain natriuretic peptide; RBBB=right bundle branch block; RWT=relative wall thickness.



Central Figure. Relative importance of AF risk factors in patients with AF onset <60 years and ≥60 years, based on counts of AF risk factors in both age groups. Abbreviations: AF=atrial fibrillation; eGFR=estimated glomerular filtration rate.

Echocardiographic differences between young and older patients.

Young onset AF patients less often had LV hypertrophy and LV remodeling (**Table 1**). Young patients also had less often diastolic dysfunction (54% vs. 88%, p<0.001) and enlarged left atrial volume index >34 ml/m^2 (39% vs. 55%, p=0.04), and left atrial reservoir and conduit function were better in young vs. older patients (respectively 31±9 vs. 26±9, p=0.003 and 18±7 vs. 14±6, p<0.001).

Echocardiographic differences including diastolic function measurements between young and older patients were similar in men and women. Although differences in atrial and ventricular remodeling seemed most pronounced in women in direct comparisons, no significant interactions of age and sex were observed (**Supplementary Tables 1 and 2**).

Symptoms according to age of AF onset.

Young patients were more often symptomatic (92% vs. 81%, p=0.02), predominantly palpitations (82% vs. 69%, p=0.04). No sex-specific differences in these associations were found.

Comparisons with very young AF patients <40 years.

Additional analyses compared very young patients <40 years (n=19) to patients 40-60 years (n=101) and ≥60 years. Younger age of AF onset was associated with lower prevalence of female sex, but higher prevalence of cardiomyopathies (p for trend respectively 0.03 and <0.001; **Figure 1A**). Higher age of AF onset was associated with hypertension, also compared to controls (p for trend <0.001; **Figure 1B**). Prevalence of familial AF was

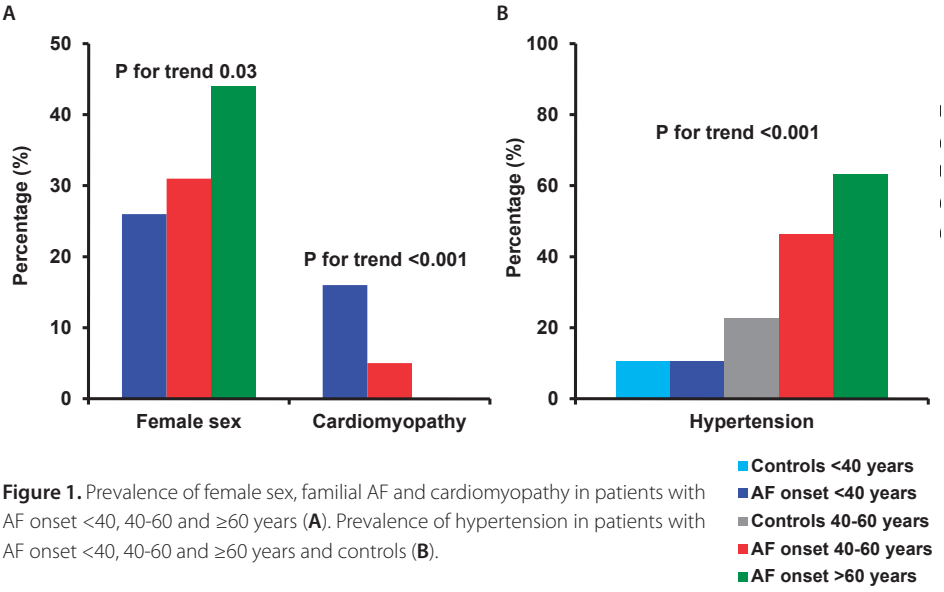


Figure 1. Prevalence of female sex, familial AF and cardiomyopathy in patients with AF onset <40, 40-60 and ≥60 years (**A**). Prevalence of hypertension in patients with AF onset <40, 40-60 and ≥60 years and controls (**B**).

comparable in both younger age groups, but higher than in patients aged ≥60 years (respectively 26% vs. 29% vs. 12%, p=0.002). Although numbers were small, relations of younger age with less atrial and ventricular remodeling persisted in these analyses.

Table 2. Characteristics of patients with AF onset < 60 years, comparison with age- and sex-matched controls from PREVEND.

	AF onset <60 yr (n=120)	Controls <60 yr (n=120)	P-value
Age (years)	51 (44-54)	51 (44-54)	1.00
Women	36 (30)	36 (30)	1.00
Heart failure	5 (4)	-	0.06
Hypertension	49 (41)	25 (21)	0.001
Diabetes mellitus	9 (8)	5 (4)	0.27
Previous myocardial infarction	4 (3)	1 (1)	0.37
Stroke	5 (4)	1 (1)	0.21
Peripheral artery disease	-	2 (2)	0.25
Physical examination:			
Height (cm)	182±10	176±8	<0.001
Height (cm; women)	172±7	169±7	0.17
Height (cm; men)	186±8	178±6	<0.001
Weight(kg)	94±17	81±12	<0.001
BMI (kg/m^2)	28.4±4.8	26.3±3.8	<0.001
Obesity	41 (34)	18 (15)	<0.001
Systolic blood pressure (mmHg)	126±19	128±17	0.32
Diastolic blood pressure (mmHg)	80±11	76±9	0.001
Electrocardiogram			
Heart rate (in sinus rhythm)	66±11	69±10	0.04
PR interval (ms)	161±26	158±19	0.23
PR interval >200ms	8 (7)	2 (2)	0.047

Data is expressed as mean±standard deviation(SD), median(IQR) or numbers(%).
Abbreviations: AF=atrial fibrillation; BMI=body mass index; NT-proBNP=N-terminal prohormone of brain natriuretic peptide.

DISCUSSION

We demonstrate that compared to older patients, young AF patients were more often men, being taller, with less often hypertension, lower NT-proBNP plasma levels and less signs of left atrial and ventricular remodeling and diastolic dysfunction, but more familial clustering of AF and cardiomyopathies. Obesity was highly prevalent in both age groups. Compared to age and sex-matched controls, young AF patients more often

had hypertension and obesity, and young AF men were taller. Finally, in both groups the prevalence of lone AF was low.

Sex differences.

Young AF patients were more often men. Also, young men with AF were taller than older AF men and controls, while no such differences were found in women. The finding that young AF patients are more often men than older patients is consistent with data from population based studies.(4,19) This difference diminished with increasing age of the population. (4,19) Tall stature has also been associated with incident AF before, probably through anatomically larger atria.(3) Differences in age of onset between sexes may possibly relate to different patterns of cardiac gene expression that make men more prone to AF at younger age, or alternatively protect young women from AF at younger age.(20) A previous study showed that electrophysiological differences exist between premenopausal women, post-menopausal women and age-matched men, which may protect young women against AF through influence of estrogen.(21)

Hypertension, left ventricular remodeling and diastolic dysfunction.

Hypertension is one of the most prevalent risk factors for AF, both in men and in women. (3,4,19, 22) Prevalence of hypertension in young AF patients was 41%, which was higher than in controls, but lower than in older patients. Hypertension may lead to left ventricular hypertrophy and diastolic dysfunction, both of which have also been identified as AF risk factors.(3,23) LV hypertrophy and LV remodeling were present in 20% of young patients versus 40% in older patients. Although direct comparisons suggested differential relations of LV remodeling with age in men and women, no significant interactions of sex and age were found.

Young patients also had better diastolic function, lower indexed atrial volumes, better atrial function and lower NT-proBNP. The younger age itself and the lower prevalence of hypertension in young patients are the most likely contributors to these findings. (23) Still, atrial function has been reported to be worse than in controls.(24) Diastolic dysfunction and atrial remodeling are well known risk factors for AF, though less established than other clinical risk factors.(3) Using 2D atrial strain we were able to show that older patients had impaired atrial compliance. Impaired atrial function may be one of the first markers of atrial remodeling, even occurring before left atrial dilatation.(15)

Obesity and physical exercise.

Obesity was highly prevalent in both young and older AF patients (prevalence ~30%), and young patients were more often obese than controls. Obesity often co-exists with other cardiovascular risk factors and diseases (e.g. hypertension, diabetes, diastolic dysfunction, sleep apnea, sedentary lifestyle), but may also increase AF risk by itself

through pro-inflammatory and pro-fibrotic effects of epicardial fat, and even infiltration of epicardial fat into the atrial myocardium.(7,8,25,26) Importantly, obesity may be a modifiable risk factor. It was recently shown that strict weight reduction diminished AF burden, atrial remodeling and left ventricular mass.(27,28) Recently, we showed that the population attributable risk of obesity for incident AF was 9%.(7) Theoretically this would mean that incidence of AF could be reduced with 9% if the risk factor obesity could be completely eliminated.(7)

Not unexpectedly, young patients more often performed regular physical activity for longer durations of time.(29,30) Only a few patients had a history of intensive exercise being comparable between both groups. Previous studies showed that both lack of and intensive physical exercise may increase AF risk, while moderate physical activity protected people from AF (U-shaped curve).(3,29-35) It is thought that increased risk of AF in physical inactive individuals may be mediated through obesity-related effects, low cardiorespiratory fitness level and other associated risk factors.(7,8,27,36) On the other hand, intensive exercise may possibly cause AF through vagal stimuli and/ or increased filling pressures during exercise and subsequent atrial remodeling.(3,33-35) In a rat model atrial fibrosis was present after 16 weeks of intensive exercise. This fibrosis did not regress after cessation of exercise. This suggests that exercise induced fibrosis may be a contributor to the occurrence of AF in patients performing intensive exercise.(37) Counseling patients with respect to exercise recommendations seems important since both too little and too much exercise may increase risk of AF. Moderate physical exercise may protect against AF, through weight loss but also through improving cardiorespiratory fitness and reversed structural remodeling.(28,36) Increased awareness of the benefits and risks of physical exercise may help prevent AF, and possibly improve cardiovascular outcomes.(27,36,38)

Family history of AF and associations with cardiomyopathies in young AF patients.

Our results indicate that family history of AF is more common in young-onset AF patients. This corresponds to previous data showing that family history of AF was associated with increased risk of developing AF, but also with younger age of AF onset.(39,40) Several genetic variants or mutations associated with AF may directly lead to AF, or may cause AF through cardiovascular risk factors and cardiomyopathies.(41,42) Young AF patients also more often had cardiomyopathies. A previous study reported that 17% of families with familial AF also presented with dilated cardiomyopathy.(40) In our study, no such association could be found.

Nevertheless our results underline the need for systematic and thorough evaluation of young, seemingly 'lone' AF patients.(11,43) Remarkably, thorough evaluation of AF risk factors in our study lead to a prevalence of lone AF as low as 2%.(11)

Limitations.

In the present cross-sectional analysis we describe differences in clinical risk profile between patients with AF occurring at young and older age. Our analyses were limited to patients without previous pulmonary vein isolation to provide optimal comparison of cardiovascular risk factors and echocardiographic measurements between both age groups. Future studies in larger patient populations will involve associations of the present phenotypical descriptions with genetic profiles, and associations with cardiovascular outcome.

CONCLUSIONS

In the present well characterized cohort young onset AF patients had a high prevalence of AF risk factors. Young AF patients were less often women, had less hypertension and a less diastolic-dysfunction related risk profile than in older patients. Instead, young onset AF was associated with taller height in men and a relatively high prevalence of familial AF and cardiomyopathies. Lone AF was very rare. Thus, AF starting at younger age is associated with a distinguishable risk profile. This may have implications for therapeutic strategies.

PERSPECTIVES

Competency in Medical Knowledge.

AF is increasingly diagnosed at young age, before the age of 60 years. Even in young patients, AF is accompanied with a high prevalence of AF risk factors and comorbidities, including obesity. However distinguishable clinical profiles exist according to age of AF onset. Younger patients were more often men with familial AF, who less frequently suffered from hypertension and diastolic dysfunction.

Translational Outlook.

More research should be directed toward understanding differences in clinical profiles according to age of AF onset. Better understanding of underlying disease may ultimately provide better patient-tailored therapy.

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SUPPLEMENT

Supplementary Table 1. Differences between young and older patients, analyzed separately in women and men.

Men	AF onset < 60yr (n=84)	AF onset ≥ 60yr (n=67)	P-value
Hypertension	33 (39)	43 (64)	0.002
Diabetes mellitus	7 (8)	14 (21)	0.03
Vascular disease	9 (11)	18 (27)	0.010
Peripheral artery disease	-	4 (6)	0.04
Cardiomyopathy	4 (5)	-	0.13
Familial AF	20 (24)	6 (9)	0.009
Height (cm)	186±8	180±7	<0.001
Weight (kg)	97±17	89±15	0.007
BMI (kg/m^2)	28 ± 4	28 ± 4	0.83
Obesity	25 (30)	19 (28)	0.91
Systolic blood pressure (mmHg)	126±19	131±14	0.09
Physical activity ≥3 times per week	27 (32)	15 (22)	0.04
Physical activity >60 min per activity	16 (19)	6 (9)	0.03
Other ECG abnormalities	8 (10)	5 (8)	0.65
Left atrial parasternal long axis (mm)	40±6	42±6	0.39
Left atrial volume index (ml/m2)	32 (25-40)	36 (26-40)	0.34
Left atrial volume index>34 ml/m2	43	54	0.22
LV mass index (g/m^2)	80 (71-94)	83 (71-94)	0.63
LV hypertrophy or remodeling	17 (20)	22 (32)	0.04
Concentric LV remodeling	13 (16)	15 (22)	0.19
Concentric LV hypertrophy	2 (2)	5 (8)	0.14
Eccentric LV hypertrophy	2 (2)	2 (3)	1.00
Diastolic dysfunction	53	82	0.005
LA reservoir function (%)	30±8	27±7	0.06
LA contraction function (%)	12±4	13±5	0.79
LA conduit function (%)	18±7	14±5	0.01
Women	**(n=36)**	**(n=53)**	**P-value**
Hypertension	16 (44)	33 (62)	0.10
Diabetes mellitus	2 (6)	4 (8)	1.00
Vascular disease	4(11)	7(13)	1.00
Peripheral artery disease	-	1 (2)	1.00
Cardiomyopathy	4 (11)	-	0.02
Familial AF	14 (39)	8 (15)	0.006
Height (cm)	172±7	170±7	0.37

Supplementary Table 1. Differences between young and older patients, analyzed separately in women and men. (continued)

Women	AF onset < 60yr (n=36)	AF onset ≥ 60yr (n=53)	P-value
Weight (kg)	87±16	81±13	0.06
BMI (kg/m^2)	30± 6	28 ± 5	0.16
Obesity	16 (44)	15 (28)	0.13
Systolic blood pressure (mmHg)	125±19	136±18	0.004
Physical activity ≥3 times per week	10 (28)	9 (17)	0.13
Physical activity >60 min per activity	10 (28)	2 (4)	0.001
Other ECG abnormalities	5 (14)	1 (2)	0.04
Left atrial parasternal long axis (mm)	35±5	39±5	0.007
Left atrial volume index (ml/m2)	31±8	37±12	0.018
Left atrial volume index >34 ml/m2	31	55	0.048
LV mass index (g/m^2)	69 (60-80)	78 (71-88)	0.01
LV hypertrophy or remodeling	7 (19)	26 (49)	0.002
Concentric LV remodeling	5 (14)	20 (38)	0.007
Concentric LV hypertrophy	-	5 (9)	0.07
Eccentric LV hypertrophy	2 (6)	1 (2)	0.57
Diastolic dysfunction (%)	55	95	<0.001
LA reservoir function (%)	32±9	26±10	0.009
LA contraction function (%)	12±5	12±5	0.91
LA conduit function (%)	20±7	14±7	0.001

Data is expressed as mean±standard deviation(SD), median(IQR) or numbers(%).
Abbreviations: AF=atrial fibrillation; BMI=body mass index; ECG=electrocardiogram; LA=left atrium; LV=left ventricle.

Supplementary Table 2. Sex-age interactions in variables with possible sex-related differences between young and older individuals (performed in total group of young and older AF patients (N=240)).

Dependent variable	P-value for age-sex interaction
Hypertension	0.60
Diabetes mellitus	0.47
Vascular disease	0.25
Peripheral artery disease	1.00
High alcohol use	0.88
Cardiomyopathy	1.00
Height	0.01
Weight	0.80
eLog BMI	0.32
Obesity	0.27
eLog systolic bloodpressure	0.15
Physical activity ≥3 times per week	0.98
Physical activity >60 min per activity	0.16
Other ECG abnormalities	0.14
LA parasternal long axis	0.14
eLog left atrial volume index	0.28
Left atrial volume index >34ml/m2	0.38
LV end-diastolic diameter index	0.41
eLog LV mass index	0.09
Relative wall thickness	0.08
LV hypertrophy or remodeling	0.23
Concentric LV remodeling	0.20
Concentric LV hypertrophy	0.99
Eccentric LV hypertrophy	0.40
Diastolic dysfunction	0.17
LA reservoir(%)	0.22

Model includes age divided in age of AF onset <60 years and age >60 years, sex and interaction term sex * age of AF onset (<60 years or >60 years).

Logistic regression was used for binominal dependent variables, linear regression for continuous dependent variables.

Abbreviations: AF=atrial fibrillation; BMI=body mass index; ECG=electrocardiogram; LA=left atrium; LV=left ventricle.

PART II

Risk factors for atrial fibrillation progression

Chapter 5

Asymptomatic Persistent Atrial Fibrillation and Outcome – Results of the RACE study

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ABSTRACT

Background.

Symptoms are a major driver for patients with atrial fibrillation (AF) to seek medical attention, and are important to titrate AF therapies. However, a large proportion of AF patients are asymptomatic.

Objective.

To investigate the clinical profile and prognosis of patients with asymptomatic recurrent persistent AF in the RACE study.

Methods.

Patients with asymptomatic AF (n=157, 30%) were compared to the 365(70%) symptomatic AF patients. The primary endpoint was a composite of cardiovascular morbidity and mortality.

Results.

Patients with asymptomatic AF were younger, and more often men than symptomatic patients. Cardiac diseases were less common. Quality of life(SF-36) was better in asymptomatic AF patients, and comparable to healthy controls. At baseline and during follow up, there were no differences in rate control, antiarrhythmic or anticoagulant drugs, cardioversions, and time in sinus rhythm. After a follow-up of 2.3±0.6 years, the primary endpoint occurred in 21(13%) asymptomatic AF patients and 83(23%) symptomatic AF patients. After adjusting for relevant covariates, asymptomatic AF was associated with a lower risk of the primary endpoint (hazard ratio 0.51, 95% confidence interval 0.29-0.92, p=0.024). This difference was driven by significantly less heart failure hospitalizations (0 versus 21[6%], and severe effects of antiarrhythmic drugs or digoxin (1[0.6%] versus 13[4%]). Importantly, no difference in the occurrence of thromboembolic complications was observed.

Conclusion.

Patients with asymptomatic AF were more often men and had less cardiac disease. During follow-up, in asymptomatic AF patients heart failure hospitalizations and severe adverse effects of antiarrhythmic and rate control drugs occurred significantly less frequently.

INTRODUCTION

Atrial fibrillation (AF) may be accompanied with symptoms, impaired quality of life, and an increased risk of stroke, dementia, heart failure and death.(1) Although most patients with AF have symptoms, approximately 15 to 30 percent of the patients diagnosed with clinical AF appear asymptomatic.(2,3) In pacemaker and ICD patients without a clinical diagnosis of AF, but at risk for AF, the incidence of (short) episodes of high atrial rates and silent AF is even higher.(4,5) At present it remains uncertain why some patients with AF are asymptomatic and others are symptomatic, and whether presence of symptoms is associated with prognosis. It has been observed, that in patients at older ages, symptoms may decrease or disappear with longer durations of the arrhythmia.(2,3,6) Somatic, psychological factors, and presence of other cardiovascular conditions that may present with similar symptoms or aggravate symptoms are likely to contribute to the complex relation between symptoms and AF.(3,7) The latest European Society of Cardiology guidelines identifies 'asymptomatic AF' as a specific clinical form, and recommends classification using the European Heart Rhythm Association (EHRA) AF-related symptom score.(1,8) Classification of AF according to symptom burden is important since large randomized trials have demonstrated that outcome of rate versus rhythm control therapies is similar,(9,10) and choice for a rate or rhythm control treatment strategy is largely driven by the degree of AF-related symptoms. Also, symptom burden is important to guide therapy and evaluate success of especially rhythm control strategies.

At present, it is uncertain whether simple awareness of symptoms can be used as prognostic marker for specific cardiovascular outcomes in patients known and treated for AF. We sought to investigate potential differences in clinical profile and prognosis of asymptomatic and symptomatic patients with recurrent persistent AF, as included in the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study.(10)

METHODS

Study design.

Study design, patient characteristics and results of the RACE study have been published previously.(10) In short, 522 patients (157 patients [30%] with asymptomatic AF) with recurrent persistent AF were included and randomized to rate or rhythm control. Patients were followed for at least two years with a maximum of three years. The follow-up scheme is described in **Supplementary Methods**.

Administration of a beta-blocker, a nondihydropyridine calcium-channel blocker, or digitalis, alone or in combination, was used to achieve rate control. The target was a

resting heart rate of less than 100 beats per minute. Patients assigned to rhythm-control underwent serial electrocardioversions and institution of serial antiarrhythmic drugs, i.e. sotalol, class IC antiarrhythmic drugs and amiodarone. Cardioversion was performed under adequate anticoagulation (target international normalised ratio (INR) 2.5 to 3.5). According to the 2001 AF guidelines,(11) all patients received acenocoumarol or fenprocoumon, unless sinus rhythm was achieved for more than 4 weeks, or when rate-control treated patients were less than 65 years old and had no underlying heart disease. In these instances, aspirin (80 to 100 mg daily) was allowed. Echocardiographic measures are published previously, and are detailed in **Supplementary Methods**.

Atrial fibrillation-related symptom assessment.

At baseline, patients were asked about symptoms during AF within the last 6 months with a 7-item symptom checklist, which was part of the case report form. These symptoms included palpitations, dyspnea, fatigue, chest pain, dizziness, syncope, or other symptoms. If at least 1 of these symptoms was present, the patient was considered to be symptomatic. Asymptomatic patients had none of these symptoms.

Primary end point.

The primary end point was the composite of death from cardiovascular cause, heart failure, thromboembolic complications, bleeding, severe adverse effects of antiarrhythmic drugs and the need for a pacemaker implantation. All events that occurred between randomization and the end of study were recorded. Definitions of the composite of the primary endpoint are described in **Supplementary Methods**, and have been described previously.(10) A committee of experts, who were unaware of the treatment assignments, adjudicated all reported end points.

Quality of life.

Quality of life was determined using the Dutch version of the Medical Outcomes Study Short-form health survey (SF-36) questionnaire as has been described before.(12) Quality of life data was available of 352(67%) of the total population. Of these, 99 patients (28%) had asymptomatic AF. Patient characteristics of those with and without quality of life were similar (data not shown). In short, the SF-36 contains items to assess physical health (general health perception, physical functioning, role limitations due to physical problems and bodily pain), as well as mental health (social functioning, role limitations due to emotional problems, mental health and vitality). In addition, healthy age- and sex-matched controls were selected from the healthy population that served to validate the Dutch version of the SF-36 (99 healthy age-matched controls).

Statistical analysis.

Baseline descriptive statistics are the mean ± standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups, in terms of patient characteristics and quality of life at baseline, and end of study, were evaluated by Students t-test or Mann-Whitney U-test, depending on normality of the data, for continuous data. For categorical data predominantly the Fisher's exact test (in case of binomial proportions) was used, in case of more than 2 response categories, Chi-square test was used. Kaplan Meier estimates and Cox proportional hazard regression analyses were performed to study the association between asymptomatic AF and the primary endpoint over time in the study population. Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. Briefly, we conducted a series of 7 models. Specific covariates are denoted in **Supplementary Methods**. Models range from unadjusted to multivariable-adjusted.
In all analyses a value of $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics.

At randomization, 157 of 522 patients (30%) had asymptomatic persistent AF. The other 365 patients (70%) had at least one AF-related symptom: palpitations (n=143, 39%), dyspnea (n=185, 51%), fatigue (n=207, 57%), angina pectoris (n=34, 9%), presyncope (n=13, 4%), or other complaints (n=73, 20%). Patients with asymptomatic AF were younger, and more often men (**Table 1**). Concomitant cardiovascular conditions as coronary artery disease and cardiomyopathy were less common in asymptomatic AF patients, and the mean $CHADS_2$ score was lower. The distribution of $CHADS_2$ scores in patients with asymptomatic and symptomatic AF is shown in **Figure 1**. Left ventricular dimensions were smaller and fractional shortening was higher in patients with asymptomatic AF. Of the asymptomatic AF patients, 49% were randomised to rate control and 51% to rhythm control. Of the symptomatic AF patients, 51% were randomised to rate control and 49% to rhythm control (p=1.0). Patients with asymptomatic AF were less frequently treated with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers, diuretics, and cholesterol lowering drugs (**Supplementary Table 1**). There were no other medication differences.

Follow-up.

Mean follow-up was 2.3±0.6 years. There were no differences between rate control drugs, antiarrhythmic drugs or anticoagulant/antiplatelet therapy between asymptomatic and symptomatic AF at the end of follow up (**Supplementary Table 1**). The baseline lower

incidence of ACE inhibitor, angiotensin-receptor blocker, diuretic, and cholesterol lowering drug use in asymptomatic AF patients, remained present at end of follow up. There were no differences between the number of electrical and chemical cardioversions that patients received during follow-up in both groups. Also, no differences were found in the time during follow up that patients were in sinus rhythm.

Table 1. Baseline characteristics of the patients according to the presence of symptoms.

Patient characteristics	Asymptomatic AF patients (n=157)	Symptomatic AF patients (n=365)	P-value
Age(years)	67±9	69±9	0.010
Male sex	113(72%)	217(60%)	0.007
Total AF duration(days)	445(17-6,465)	462(1-14,909)	0.61
Duration present episode of AF(days)	36(1-392)	32(1-399)	0.48
Coronary artery disease	25(16%)	118(32%)	<0.001
Old myocardial infarction	17(11%)	61(17%)	0.11
Valve disease	21(13%)	66(18%)	0.20
Cardiomyopathy	8(5%)	39(11%)	0.045
History of hypertension	67(43%)	189(52%)	0.07
Heart failure NYHA class II/III	37(34%)	224(61%)	<0.001
No heart disease	50(32%)	58(16%)	<0.001
History of chronic obstructive pulmonary disease	17(11%)	60(16%)	0.28
Diabetes mellitus	14(9%)	39(11%)	0.64
Previous ischemic thromboembolic complication	23(15%)	50(14%)	0.78
$CHADS_2$ score	1.2±1.1	1.7±1.1	<0.001
Heart rate(rest)(bpm)	89±20	91±21	0.29
Blood pressure(mmHg)			
Systolic	142±21	144±22	0.26
Diastolic	85±11	85±11	0.61
Echocardiographic measurements			
Size of left atrium, long axis(mm)	44±7	45±7	0.26
Size of left atrium, apical view(mm)	64±8	63±9	0.30
Size of right atrium, apical view(mm)	58±8	57±8	0.37
Left ventricular end-diastolic diameter(mm)	51±6	53±7	0.004
Left ventricular end-systolic diameter(mm)	35±7	38±9	0.001
Septal thickness(mm)	10±2	10±3	0.85
Posterior wall thickness(mm)	10±2	10±2	0.28
Fractional shortening(%)	32±9	30±10	0.041

Abbreviations: AF=atrial fibrillation; $CHADS_2$=stroke risk index(NYHA functional class II/III at baseline, hypertension, age >75 years, diabetes, and history of stroke); NYHA=New York Heart Association functional classification of heart failure.

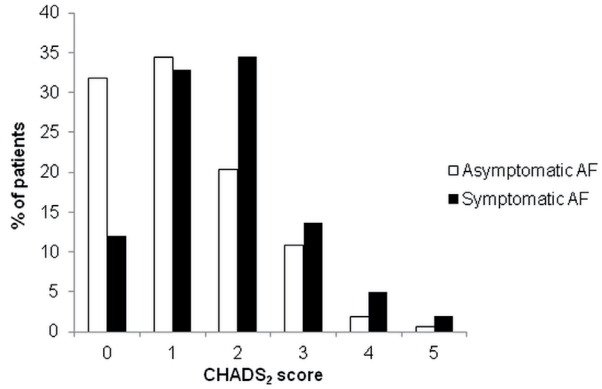

Figure 1. $CHADS_2$ score distribution in patients with asymptomatic and symptomatic AF.

Quality of life.

By definition, asymptomatic AF patients had no AF-related symptoms and had better quality of life (**Figure 2**). On all 8 scales of the SF-36 questionnaire, asymptomatic AF patients had higher quality of life scores. Quality of life of asymptomatic AF patients was comparable to age- and sex-matched controls, except for the bodily pain subscale, which was higher in asymptomatic AF patients than in healthy controls (**Figure 2**).

Table 2. Incidence of the primary end point and its components according to presence of symptoms.*

End point – n (%)	Asymptomatic AF patients (n=157)	Symptomatic AF patients (n=365)	Absolute difference (95% CI)	P-value
End point	19(12%)	85(23%)	-11.2(-18.5 to -3.8)	0.003
Death from cardiovascular causes	8(5%)	28(8%)	-2.6(-7.1 to 2.0)	0.27
Sudden death	3(2%)	13(4%)		
Heart failure	3(2%)	2(0.5%)		
TEC	-	6(2%)		
Bleeding	2(1%)	7(2%)		
Heart failure	-	21(6%)	-5.8(-8.2 to -3.3)	<0.001
Thromboembolic complications	9(6%)	26(7%)	-1.4(-6.0 to 3.2)	0.56
Bleeding	6(4%)	15(4%)	-0.3(-4.0 to 3.4)	0.88
Severe adverse effects of AAD	1(0.6%)	13(4%)	-2.9(-5.2 to -0.6)	0.013
Pacemaker implantation	2(1%)	9(2%)	-1.2(-3.6 to 1.2)	0.33

*Some patients had more than one end point.

Abbreviations: AAD=antiarrhythmic drugs; AF=atrial fibrillation; CI=confidence interval; TEC=thromboembolic complications.

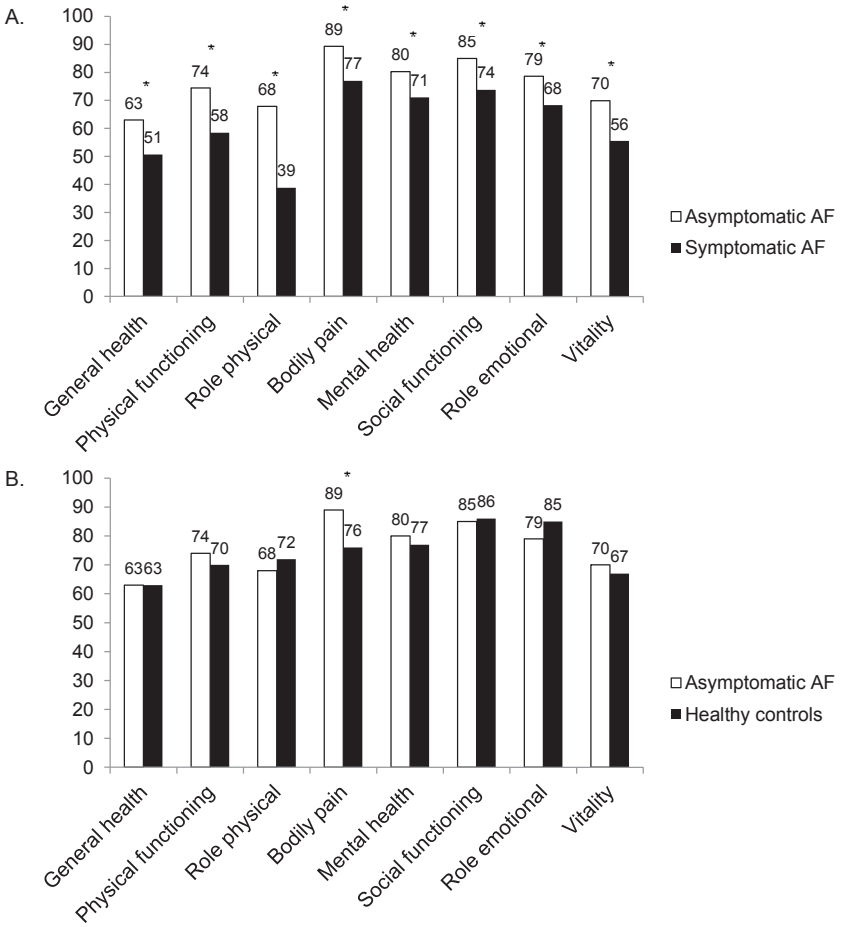

Figure 2. Quality of life comparison at baseline according to the presence of symptoms, and compared with age- and sex-matched healthy controls. *p<0.05 Asymptomatic AF versus symptomatic AF (**2A**); Asymptomatic AF versus healthy controls (**2B**).

Cardiovascular morbidity and mortality.

The composite primary end point occurred in 19(12%) asymptomatic AF patients and 85(23%) symptomatic AF patients (p=0.003; **Table 2,** and **Figure 3**). Patients with asymptomatic AF were not hospitalized for heart failure (0 versus 21[6%], p<0.001, in asymptomatic and symptomatic AF, respectively), and significantly less severe effects of antiarrhythmic drugs or digoxin (1[0.6%] versus 13[4%], p=0.013 in asymptomatic and symptomatic AF, respectively), occurred. One patient with asymptomatic AF developed a high-degree atrioventricular block, all other severe adverse events occurred in symptomatic AF patients (6 patients had sick sinus syndrome or atrioventricular block; 3 had torsade de pointes or ventricular fibrillation; 1 had rapid, hemodynamically significant

Table 3. Relation of asymptomatic AF and the occurrence of the primary end point using Cox regression analyses.

	Asymptomatic AF	
	Hazard ratio (95% confidence interval)	**P-value**
Model 1	0.43(0.26-0.71)	0.001
Model 2	0.46(0.27-0.76)	0.003
Model 3	0.46(0.28-0.77)	0.003
Model 4	0.51(0.30-0.86)	0.011
Model 5	0.55(0.32-0.97)	0.038
Model 6	0.53(0.30-0.91)	0.021
Model 7	0.51(0.29-0.92)	0.024

Model 1= unadjusted;
Model 2= age and sex adjusted;
Model 3= age, sex, randomised treatment adjusted,
Model 4= age, sex, randomised treatment, $CHADS_2$ adjusted;
Model 5= age, sex, randomised treatment, NYHA class II or III, hypertension, diabetes, previous TEC, coronary artery disease, valvular disease, total AF duration adjusted;
Model 6= age, sex, randomised treatment, $CHADS_2$, coronary artery disease, valvular disease, total AF duration+medication* adjusted;
Model 7= age, sex, randomised treatment, $CHADS_2$, coronary artery disease, valvular disease, total AF duration+echocardiographic measurements† adjusted.
*Medication=ACE inhibitor, angiotensin receptor blockers, cholesterol lowering drugs, diuretics.
†Echocardiographic measurements=fractional shortening, parasternal left atrial diameter, left-ventricular end diastolic diameter.
Abbreviations: AF=atrial fibrillation; $CHADS_2$=stroke risk index(NYHA functional class II/III at baseline, hypertension, age >75 years, diabetes, and history of stroke); NYHA=New York Heart Association functional classification of heart failure; TEC=thromboembolic complications.

atrioventricular conduction during flutter; 2 had nonlethal digoxin intoxication and 1 had drug-induced heart failure). The other components of the primary end point, including the occurrence of the thromboembolic complications, were not statistically different between both groups. After multivariable adjustments, asymptomatic AF was associated with a lower risk of the primary endpoint (hazard ratio 0.51, 95% confidence interval 0.29-0.92, p=0.024; **Table 3**). In secondary analyses, we analyzed the absence of each individual symptom and its relation with occurrence of the primary endpoint. The subgroups of patients with individual symptoms were small, and the number of endpoints was low in each subgroup. Although not all associations were significant, the hazard ratios were almost all in the same direction, except for angina pectoris (n=34, 4%; **Supplementary Table 2**).

Discussion

In the present post-hoc analysis of the RACE study(10) we observed that patients with asymptomatic persistent AF had less cardiovascular diseases, and the composite primary

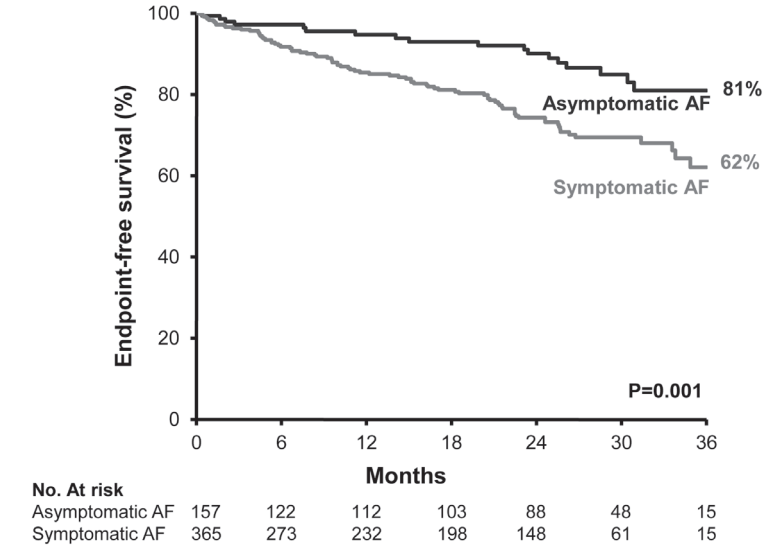

Figure 3. Kaplan Meier curve according to the presence of symptoms.

end point, mainly driven by heart failure hospitalizations and severe adverse effects of antiarrhythmic and rate control drugs occurred less frequently than in symptomatic AF patients. In multivariate analysis after adjusting for differences in clinical characteristics, medication use, and echocardiographic measurements this difference remained present. Importantly, no difference in the occurrence of thromboembolic complications between both groups was observed.

Prevalence of asymptomatic AF.

Of the total number of patients with recurrent persistent AF included in the RACE study, 30% had no AF-related symptoms and were diagnosed as asymptomatic AF. In the literature the frequency of asymptomatic AF varies widely and depends on the studied population, the temporal pattern of AF (paroxysmal, persistent or permanent), and the method of detection.(2-6,13) The frequency of silent AF varies between 10 and 50%, and within the same patient symptomatic and asymptomatic episodes may occur.(2-6) The detection of the actual rhythm is more complicated in patients with paroxysmal AF, and is therefore probably underestimated since symptomatic and asymptomatic AF episodes frequently occur in the same patient.(4,5) In patients at more advanced ages with longer durations of AF, as is the case in patients with persistent or permanent AF, symptom burden may decrease.(2,3,6,14)

Clinical profile of asymptomatic persistent AF.

Patients with asymptomatic persistent AF have a different clinical profile than patients with AF-related symptoms. Firstly, more men were asymptomatic. This consistent with prior studies, including a prior study of the RACE cohort and more recently in the Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison between Lenient and Strict Rate Control II (RACE II) study, where women had more AF-related symptoms and more impaired quality of life than men.(15,16) Whether this is caused by differences in age and comorbidities,(15,17) differences in disease coping and disease burden,(18,19) or differences in the incentive to seek medical attention is not completely understood.(20) Secondly, we found less (severe) cardiac diseases in asymptomatic AF patients, and as a consequence less use of ACE inhibitors, angiotensin receptor blockers, diuretics and cholesterol lowering drugs. Specifically, we found no differences in use of negative dromotropic drugs or antiarrhythmics, or anticoagulant therapies, and the application of a rate or rhythm control strategy was distributed evenly. However, we were not informed on dosages of medications applied. Our results are in accordance with the results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial, in which 481 of the total 4060 patients (12%) with paroxysmal or persistent AF were asymptomatic, and had less severe cardiac disease, and received different therapies than symptomatic patients.(3) These differences in clinical profile support the notion that the underlying disease present in patients with persistent and permanent AF is a major contributing factor for the awareness of symptoms.(12) Previously, it was shown that quality of life was similar between AF patients with long-term sinus rhythm (effectively treated with rhythm control), and AF patients with permanent AF (treated with rate control).(21) More recently, the RACE II investigators demonstrated that in patients with permanent AF, stringency of heart rate control did not influence quality of life, but that among others the severity of the underlying disease influenced quality of life.(16) In addition, no differences in quality of life were found when comparing permanent AF patients treated with successful strict rate control, unsuccessful strict rate control or lenient rate control.(22) Patients with paroxysmal AF are frequently (severely) symptomatic, and mainly experience palpitations.(2) In paroxysmal AF, symptomatology seems mainly driven by the arrhythmia itself rather than by the underlying cardiac condition.(23) These patients were not included in present study.

Prognosis of asymptomatic AF.

We found that after adjusting for differences in clinical profiles of patients with asymptomatic AF and those with symptomatic AF, asymptomatic AF was related to less heart failure hospitalizations and adverse effects of antiarrhythmics and rate control drugs. However, to explain why the prognosis of asymptomatic AF *per se* is different from symptomatic AF is more challenging. Firstly, although we adjusted for relevant covariates,

patients with asymptomatic AF appear to have less cardiovascular diseases which may have led to the absence of heart failure hospitalizations. Furthermore, almost all severe adverse effects of antiarrhythmics and digoxin, occurring in symptomatic AF patients, were bradyarrhythmias, which may also be related to the presence of underlying cardiac diseases. Also, we did not find differences in negative dromotropic medication, however, we cannot exclude differences in dosages of applied therapies. Secondly, the absence of symptoms may withhold patients to more vigorous pursuit of rhythm control or rate control strategies.(7,24) Symptoms also may abate when patients are started on pharmacological therapy, in some cases despite the persistence of arrhythmia.(25) Although we did not find statistical differences in the applied therapies, we cannot exclude that absence of symptoms led to less aggressive rhythm control therapies, and may have precluded the occurrence of adverse effects of antiarrhythmic drugs in asymptomatic AF patients. Safety of antiarrhythmic drugs has always been a concern, especially in those patients with cardiac diseases, and those treated with multiple drugs.(1) In the RACE study, therapies within the rhythm control arm were left to the discretion of the treating clinician, and almost all severe adverse effects of antiarrhythmic drugs and digoxin occurred in symptomatic AF patients. Thirdly, patients with asymptomatic AF without impaired quality of life, may not be limited in their daily activities, and may therefore have a less sedentary lifestyle. This may help to avoid development or progression of heart failure. Unfortunately, we did not have exercise tests or questionnaires on daily activities in the RACE study to support this notion. Fourthly, symptomatic patients may potentially be symptomatic from disease entities other than AF, which may impact prognosis in this cohort of older aged patients. For example, chronic obstructive pulmonary disease, may cause dyspnea and fatigue, like AF, and is also proven an important factor in the progression of AF to more sustained forms.(26) Finally, the largely unknown mechanisms explaining the presence of symptoms of AF make it very difficult to explain present findings.

Limitations.

The present study was a post-hoc analysis of a randomized controlled trial, and was not designed to study differences in outcome according to the presence or absence of AF symptoms. Therefore, we cannot definitely answer whether absence of AF symptoms *per se* is directly related to a more favorable prognosis, or whether symptomatology is a marker of concomitant cardiovascular conditions. Importantly, our findings cannot be extended to individuals with untreated silent AF, as for example, included in the ASSERT study.(5) Individuals in ASSERT had no documented AF and were not treated for AF. During follow-up, a third of individuals had silent high atrial rates >6 minutes, with a rate >190 bpm, detected by a pacemaker. These individuals were at increased risk of stroke and systemic embolism. In our study, we included patients who were diag-

nosed as asymptomatic persistent AF, and were treated according to the AF guidelines, including anticoagulation treatment.(11) We found no differences in the occurrence of thromboembolic complications between both groups, although the number of thromboembolic complications was limited (35 of the 522 patients). The RACE study was performed before the era of catheter ablation for AF,(27) so our results cannot be generalized to post-ablation patients. Lastly, we did not ascertain symptom burden with one of the specific AF symptoms questionnaires,(28-31) but instead used a 7-question symptom checklist that was filled in by the treating physician. No data was available on prior symptoms before baseline.

CONCLUSION

Patients with asymptomatic persistent AF had less cardiac disease, and when treated, had less heart failure hospitalizations and severe adverse effects of antiarrhythmics and rate control drugs, compared to those with symptomatic AF. Future studies are warranted to further clarify the mechanisms underlying AF symptoms and prognosis.

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SUPPLEMENTARY METHODS

Follow-up scheme.

Patients were seen in the outpatient department 1, 3, 6, 12, and 24 months after randomization and at the end of the study. At each visit, any cardiovascular events were recorded, and a 12-lead electrocardiogram was obtained. All events had to be reported on a special form. After documentation of one (nonfatal) end point, follow-up was continued to document additional end points.

Echocardiography.

Two-dimensional transthoracic echocardiography was performed to measure left and right atrial sizes and left ventricular sizes. For the left atrium, the anteroposterior dimension was measured from the parasternal long-axis view. The superoinferior dimension of both the left and right atrium was measured the apical four-chamber view, with the transducer at the apex of the heart. All atrial measurements were taken at end-systole. Left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) were measured in the parasternal long-axis view. Fractional shortening was calculated as an estimate of left ventricular function as the difference between LVEDD and LVESD divided by LVEDD. Two-dimensional and color Doppler imaging were performed to screen for valvular stenosis or regurgitation.(1)

Composites of the primary endpoint.

Heart failure was defined as an episode of left or right ventricular failure necessitating hospitalization. Cerebrovascular events had to be diagnosed by a neurologist, and the cause was determined with the use of computed tomography. Peripheral thromboembolism had to be confirmed by a surgeon. Bleeding was recorded as an end point if the hemoglobin value decreased by more than 2 g per liter, if blood transfusion or hospitalization was necessary, or if the bleeding was fatal. Torsade de pointes, unexpected ventricular tachycardia or fibrillation, 1:1 atrioventricular conduction during atrial flutter, third-degree atrioventricular block, the sick sinus syndrome, digitalis intoxication, and drug-induced heart failure were classified as severe adverse effects of antiarrhythmic drugs, as has been described previously.(2)

Specific covariates in multivariate analyses.

Model 1 was unadjusted, **Model 2** age- and sex-adjusted; **Model 3** was age, sex, and randomized treatment-adjusted, **Model 4** was age, sex, and randomized treatment, and $CHADS_2$ (NYHA functional class II/III at baseline, hypertension, age > 75 years, diabetes, and history of stroke/TIA) score-adjusted, **Model 5** was age, sex, randomized treatment, NYHA functional class II or III, hypertension, diabetes, previous thromboembolic

complications, coronary artery disease, valvular disease, total AF duration (calculated from first diagnosis of AF to baseline of present study) adjusted, **Model 6** was age, sex, randomized treatment, $CHADS_2$, coronary artery disease, valvular disease, total AF duration, and medication (ACE inhibitor, angiotensin receptor blockers, cholesterol lowering drugs, diuretics) adjusted, and finally, **Model 7** was age, sex, randomized treatment, $CHADS_2$, coronary artery disease, valvular disease, total AF duration, echocardiographic measurements (fractional shortening, parasternal left atrial diameter, left-ventricular end diastolic diameter) adjusted.

Supplementary Table 1. Treatment at baseline, and treatment and rhythm during follow-up according to the presence of symptoms.

	Asymptomatic AF patients (n=157)	Symptomatic AF patients (n=365)	P-value
Baseline			
Beta blocker alone	17(11%)	24(7%)	0.11
Diltiazem or verapamil alone	11(7%)	22(6%)	0.70
Digoxin alone	51(33%)	133(36%)	0.43
Beta blocker and diltiazem or verapamil	3(2%)	8(2%)	1.00
Beta blocker and digoxin	15(10%)	36(10%)	1.00
Diltiazem or verapamil and digoxin	19(12%)	50(14%)	0.67
Beta blocker and diltiazem or verapamil and digoxin	-	2(1%)	1.00
Class Ic antiarrhythmics	17(11%)	37(10%)	0.88
Sotalol	41(26%)	127(35%)	0.053
Diuretics	47(30%)	148(41%)	0.023
ACE and AR inhibitors	34(22%)	160(44%)	<0.001
Cholesterol lowering drugs	13(8%)	57(16%)	0.025
Anticoagulation	153(98%)	351(96%)	0.60
Aspirin	2(1%)	7(2%)	0.73
Follow-up			
Number of electrical cardioversions (median, range)	1(0-6)	1(0-11)	0.71
Number of electrical cardioversions ≤1	114(73%)	251(69%)	0.47
Number of electrical cardioversions ≥2	43(27%)	113(31%)	
>75% of study follow up in sinus rhythm	32(20%)	100(27%)	0.10
Number of chemical cardioversions (median, range)	0(0-1)	0(0-2)	0.86
End of study*			
Sinus rhythm	33(21%)	93(26%)	0.32
Beta blocker alone	25(17%)	41(12%)	0.15
Diltiazem or verapamil alone	13(9%)	26(8%)	0.72
Digoxin alone	31(21%)	72(21%)	1.00
Beta blocker and diltiazem or verapamil	1(1%)	11(3%)	0.12
Beta blocker and digoxin	17(12%)	41(12%)	1.00
Diltiazem or verapamil and digoxin	12(8%)	47(14%)	0.10
Beta blocker and diltiazem or verapamil and digoxin	4(3%)	8(2%)	0.76
Class Ic antiarrhythmics	21(14%)	36(11%)	0.28
Amiodarone	13(9%)	42(12%)	0.35
Sotalol	26(18%)	71(21%)	0.46
Diuretics	44(30%)	165(48%)	<0.001
ACE and AR inhibitors	41(28%)	183(54%)	<0.001
Cholesterol lowering drugs	16(11%)	70(21%)	0.010
Anticoagulation	123(84%)	282(83%)	0.80
Aspirin	6(4%)	23(7%)	0.30

*End of study medication data was available for 147(94%) asymptomatic patients and 342(94%) symptomatic patients.

Abbreviations: ACE= angiotensin converting enzyme; AF= atrial fibrillation; AR= angiotensin receptor.

Supplementary Table 2. Association of absence of each symptom with the primary endpoint.

	Hazard ratio (95% CI)*	P-value
Absence of fatigue	0.57(0.36-0.90)	0.016
Absence of dyspnea	0.57(0.36-0.91)	0.019
Absence of palpitations	0.89(0.56-1.41)	0.61
Absence of angina pectoris	1.72(0.76-3.89)	0.19
Absence of presyncope	0.18(0.05-0.60)	0.005
Absence of other symptoms	0.94(0.50-1.78)	0.85

*Adjusted for age, sex, randomized treatment, $CHADS_2$, coronary artery disease, valvular disease, total AF duration + echocardiographic measurements (fractional shortening, parasternal left atrial diameter, left-ventricular end diastolic diameter).
Abbreviation: CI = confidence interval.

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Chapter 6

Symptom Severity is Associated with Cardiovascular Outcome in Patients with Permanent Atrial Fibrillation in the RACE II study

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ABSTRACT

Aims.

Symptoms and symptom burden have a central place in diagnosis and management of AF. The aim of the present study is to investigate whether severity of atrial fibrillation (AF) symptoms impacts prognosis in permanent AF.

Methods.

We studied the relation between AF symptom severity (quantified with the Toronto AF Severity Scale [AFSS]) and cardiovascular outcome in patients included in the RACE II study. The primary endpoint was a composite of cardiovascular morbidity and mortality. Secondary outcome was cardiovascular hospitalizations.

Results.

Of 614 permanent AF patients in RACE II, AFSS questionnaires were available in 558 patients (91%). Mean age was 68±8 years. 174 patients (31%) reported a low score (score 0-3; lowest tertile), 190 patients (34%) reported a moderate score (score 4-9; middle tertile), and 194(35%) reported a high score (score 10-35; highest tertile). Patients with the most severe symptoms were more often women, had higher NT-proBNP concentrations, and had more previous heart failure hospitalizations. Median follow-up was 3.0 (interquartile range 2.3-3.0) years. The primary end point occurred most frequently in the highest tertile of the AFSS (16[9%], 19[10%], 36[19%], respectively, p=0.01), being mainly driven by heart failure hospitalizations (4[2%], 1[1%], 16[8%], respectively, p<0.001). After multivariable adjustment, higher AFSS scores were associated with the primary endpoint (hazard ratio 1.38[1.15-1.66], p=0.001), as well as with cardiovascular hospitalizations (hazard ratio 1.33[1.14-1.54], p<0.001).

Conclusion.

In permanent AF, after multivariable-adjustment, symptom severity is associated with cardiovascular outcome.

INTRODUCTION

Atrial fibrillation (AF) is not a benign condition.(1) It may cause symptoms, and is associated with stroke, heart failure and impaired quality of life.(1) Symptoms related to AF are the main driver to seek medical attention. Symptoms and severity of symptoms vary widely within patients and between patients with AF.(2-7) A subset of AF patients have silent (asymptomatic) AF, that often remains undetected until serious AF-related complications arise.(5,8) Symptoms are known to vary according to temporal patterns of AF (paroxysmal, persistent, or permanent AF).(2,6,9) AF registries have shown that in general, paroxysmal AF patients are most symptomatic, while permanent AF patients experience the least symptoms. Approximately 55 to 70% of permanent AF patients are symptomatic, primarily reporting dyspnea, fatigue and palpitations.(6,9,10)

Little is known about pathophysiological mechanisms and comorbidities associated with symptoms in AF.(11) Concomitant cardiovascular conditions may present with similar symptoms or may aggravate existing symptoms. In previous studies symptom burden of paroxysmal and persistent AF patients was driven by more severe underlying heart disease,(2,12) but were not associated with future cardiovascular events.(2) Symptoms may have different prognostic importance in different AF populations, because of differences in concomitant cardiovascular conditions and temporal patterns of AF. In the present analysis of the Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison between Lenient and Strict Rate Control II (RACE II) study, we investigate symptom severity in patients with short-lasting (< 1 year) permanent AF and study differences in the clinical profile and prognosis of patients with low, intermediate, or high AF symptom severity scores.

METHODS

Patient population.

The study design of RACE II has been published elsewhere.(13,14) The institutional review board of each participating hospital approved the study, and all patients provided written informed consent. In short, 614 patients were randomized to lenient rate control (resting heart rate <110 beats/min) or strict rate control (resting heart rate <80 beats/min and heart rate <110 beats/min during moderate exercise). Rate control was instituted with beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin, alone or in combination and at various doses, until the target heart rate was achieved.(13) After achievement of the rest and activity heart rate targets in the strict group, 24-hour Holter monitoring was performed to check for bradycardia. Follow-up outpatient visits occurred every two weeks until the heart rate target(s) were achieved (dose-adjustment

phase), and in all patients after 1, 2, and 3 years. Follow-up was terminated after a follow-up period of 3 years or on June 30, 2009, whichever came first.

Atrial fibrillation symptom assessment.

At baseline, the treating physician asked the patients for presence of AF-related symptoms, using a 7-question symptom checklist as part of the case report form. These symptoms included palpitations, dyspnea, fatigue, chest pain, dizziness, syncope, or other symptoms. Asymptomatic AF was defined as absence of any symptoms.

Arial fibrillation severity score.

At baseline, severity of AF-related symptoms was assessed by self-report of each patient using Part C of the University of Toronto AF Severity Scale (AFSS),(15) a disease-specific instrument intended to measure the severity of arrhythmia-related symptoms. This 7-item questionnaire includes common AF symptoms at rest (palpitations, dyspnea, fatigue, dizziness and chest pain), and during exercise (dyspnea, fatigue). In this questionnaire, severity of each symptom is rated on a 6-point scale, ranging from 0 to 5 points. Scores thus range from 0 to 35 points, with higher scores indicating greater AF symptom severity.

Outcome.

The primary outcome was a composite of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation. The secondary outcome was cardiovascular hospitalizations. Definitions of the composites of the primary end point have been described before.(13,14) All end points were adjudicated by an independent adjudication committee.(13,14)

Statistical analysis.

Descriptive statistics are presented as mean±SD or median (range) for continuous variables, and numbers with percentages for categorical variables. We evaluated differences between the tertiles of the AFSS score, at baseline and during follow-up, using the chi-square test and Fisher exact test for categorical data, and the ANOVA and Kruskal-Wallis test for continuous data, depending on whether data were normally distributed. A chi-square test for linear trend was used to examine relations between tertiles of the AFSS and individual symptoms. We used Cox proportional hazards regression to examine the association of AFSS score as a continuous variable with the primary and secondary outcomes over time in the study population. Secondary analyses evaluated the association of symptoms assessed by the physician with the primary and secondary

outcomes. Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. Hazard ratios per 5 AF severity scale points were calculated. Briefly, we conducted a series of 4 pre-specified models for the primary outcome and cardiovascular hospitalizations. Specific covariates are detailed in **Table 5.** Cumulative event proportions for tertiles of the AF severity scale were calculated using Kaplan-Meier analysis. The log-rank test was used to compare groups. In all analyses a value of $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics.

At baseline, 558 of the total of 614 patients (91%) returned the AF symptom severity questionnaire. The patient characteristics of the 56 patients without AFSS were comparable to the patients in present analysis (data not shown). The mean AFSS score was 7.8±6.3 (median 6, IQR 3-12). Of the total, 174 patients (31%) reported a low score (score 0-3; lowest tertile), 190 patients (34%) reported a moderate score (score 4-9; middle tertile), and 194 (35%) reported a high score (score 10-35; highest tertile) on the AFSS (**Table 1)**. Patients with the most severe symptoms had higher NT-proBNP concentrations and more previous hospitalizations for heart failure. Patients with the highest AFSS were more often women. At the end of the dose adjustment phase, patients in the lowest tertile more often used no rate control drugs (9%) or beta-blocker therapy alone (39%), while patients in the highest tertile more often used the combination of digoxin and verapamil (13%, **Table 2**). Patients in the highest tertile were more frequently treated with diuretics (44%). The mean duration of exercise with heart rate target achieved was shorter in patients in the highest tertile of the AFSS.

AF symptom severity scale and relation with physician-documented symptoms.

For each specific component of the AFSS the number of patients increased with each tertile of the AFSS (**Table 3**). This same trend was also observed for all physician-assessed symptoms, although less evident. In the lowest tertile, 70% of the patients were considered asymptomatic according to the physician, while this number was 18% in the highest tertile (p for trend <0.001). In the highest AFSS tertile, proportions of patients with individual physician assessed symptoms were relatively low compared to individual symptoms assessed by the AFSS score.

Follow-up.

Median follow-up was 3.0 (interquartile range 2.3-3.0) years. At the end of follow-up there were no significant differences in the use of rate control drugs (data not shown).

The baseline lower use of diuretics in patients in the lowest tertile of the AFSS score, remained present at the end of follow-up (**Table 2**). There were no differences in achieved heart rates, heart rate targets during follow-up between the three groups.

Table 1. Patient characteristics according to tertiles of the AFSS.

	Tertile 1 (N=174)	Tertile 2 (N=190)	Tertile 3 (N=194)	
AFSS score	**0-3**	**4-9**	**10-35**	**P-value**
Age – Mean±SD – year	68±8	68±8	68±9	0.85
Female sex – no. (%)	34(20%)	64(34%)	90(46%)	<0.001
Treatment – no. (%)				0.63
Strict rate control	80(46%)	92(48%)	99(51%)	
Lenient rate control	94(54%)	98(52%)	95(49%)	
NT-ProBNP – pg/ml – Median (IQR)	876 (563-1366)	973 (652-1613)	1132 (793-1836)	0.003
Creatinine – Mean±SD – micromol/L	98±22	93±20	96±26	0.12
Total AF duration – months – Median (IQR)	15(5-51)	20(6-54)	19(6-61)	0.60
Hypertension – no. (%)	116(67%)	111(58%)	118(61%)	0.25
Coronary artery disease – no. (%)	27(16%)	38(20%)	39(20%)	0.44
Valve disease – no. (%)	25(14%)	36(19%)	51(26%)	0.02
Diabetes mellitus – no. (%)	21(12%)	13(7%)	30(15%)	0.03
Previous hospitalization for heart failure – no. (%)	9(5%)	20(11%)	25(13%)	0.04
$CHADS_2$ score – Mean±SD	1.4±1.0	1.3±1.1	1.5±1.1	0.22
Functional class (NYHA) - no. (%)				<0.001
I	153(88%)	134(70%)	73(38%)	
II	20(11%)	51(27%)	100(51%)	
III	1(1%)	5(3%)	21(11%)	
Body mass index – Mean±SD – kg/m^2	28±4	29±4	29±5	0.12
Blood pressure – Mean±SD – mmHg				
Systolic	138±17	135±18	136±18	0.20
Diastolic	84±13	83±11	83±11	0.75
Heart rate in rest – Mean±SD – bpm	97±13	94±11	96±12	0.16
Heart rate > 100 in rest – no. (%)	53(30%)	42(22%)	64(33%)	0.048
Echocardiographic parameters – Mean±SD – mm				
Left atrial size, long axis	46±7	47±7	46±6	0.70
Left ventricular end diastolic diameter	51±7	51±7	51±8	0.91
Left ventricular end systolic diameter	36±7	36±8	37±9	0.57
LVEF – Mean±SD –%	53±11	53±10	51±13	0.18
LVEF ≤40%	23(14%)	22(13%)	37(21%)	0.09

Abbreviations: AF = atrial fibrillation; AFSS= AF Severity Scale; bpm= beats per minute; $CHADS_2$=stroke risk index (NYHA functional class II/III at baseline, hypertension, age >75 years, diabetes, and history of stroke); ECV=electrical cardioversion; IQR=interquartile range; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal prohormone of brain natriuretic peptide; SD=standard deviation; TEC= thrombo-embolic complications

Table 2. Rate control and drug therapy at end of dose adjustment phase and during follow-up, according to tertiles of the AFSS.

	Tertile 1 (N=174)	Tertile 2 (N=190)	Tertile 3 (N=194)	
AFSS score	**0-3**	**4-9**	**10-35**	**P-value**
Rate control targets				
Rate control targets achieved	141(81%)	157(83%)	166(86%)	0.50
Strict rate control	49/80 (61%)	60/92 (65%)	74/99 (75%)	0.13
Lenient rate control	92/94 (98%)	97/98 (99%)	93/95 (98%)	0.80
Resting heart rate end dose adjustment – Mean ± SD – bpm	86±14	85±13	84±13	0.48
Resting heart rate target achieved	150 (86%)	163 (86%)	174 (90%)	0.46
Exercise heart rate target achieved[a]	55/73 (75%)	68/83 (82%)	79/91 (87%)	0.17
Mean heart rate – bpm	101±16	99±16	97±15	0.19
Mean duration of exercise with target achieved – sec	102±52	96±43	84±34	0.03
Reason for failure to achieve rate control target or targets				0.34
Drug-related adverse events	5/33 (15%)	11/33 (33%)	8/28 (29%)	
No symptoms or tolerable symptoms	21/33 (64%)	18/33 (55%)	13/28 (46%)	
Target impossible to achieve with drugs	7/33 (21%)	4/33 (12%)	7/28 (25%)	
No. dose adjustment visits (median, IQR)	1(0-2)	1(0-2)	1(0-2)	0.34
Resting heart rate at 1 year follow-up – bpm	81±14	79±12	80±14	0.28
Resting heart rate at 2 year follow-up – bpm	80±13	78±11	79±14	0.44
Resting heart rate at end of study – bpm	80±15	79±13	81±15	0.59
Rate control medication at end of dose adjustment phase – no. (%)				
None	15(9%)	12(6%)	5(3%)	0.04
Betablocker alone	67(39%)	66(35%)	51(26%)	0.04
Verapamil or diltiazem alone	11(6%)	11(6%)	10(5%)	0.89
Digoxin alone	6(3%)	11(6%)	6(3%)	0.36
Betablocker and either verapamil or diltiazem	9(5%)	15(8%)	20(10%)	0.19
Betablocker and digoxin	49(28%)	53(28%)	53(27%)	0.98
Digoxin and either verapamil or diltiazem	8(5%)	12(6%)	26(13%)	0.004
Betablocker, digoxin and either verapamil or diltiazem	3(2%)	6(3%)	12(6%)	0.07
Dose at end of dose adjustment phase – mg (number of patients)				
Beta-blocker[b]	138±71 (130)	139±92 (141)	153±93 (139)	0.26
Verapamil	229±100 (28)	192±83 (42)	205±94 (64)	0.28
Diltiazem	267±58 (3)	210±128 (2)	204±64 (5)	0.53
Digoxin	0.20±1.0 (69)	0.20±0.8 (84)	0.19±0.7(100)	0.60
Other medication at end of dose adjustment phase – no. (%)				
ACE-inhibitors and/or angiotensin receptor blocker	88(51%)	94(50%)	100(52%)	0.92
Diuretics	54(31%)	89(47%)	86(44%)	0.005
Statin	45(26%)	57(30%)	66(34%)	0.23
Vitamin K antagonists	170(98%)	187(98%)	193(99%)	0.35
Aspirin	4(2%)	2(1%)	2(1%)	0.61

Table 2. Rate control and drug therapy at end of dose adjustment phase and during follow-up, according to tertiles of the AFSS. (continued)

	Tertile 1	Tertile 2	Tertile 3	
AFSS score	**0-3**	**4-9**	**10-35**	**P-value**
Other medication at end of study – no. (%)				
ACE-inhibitors and/or angiotensin receptor blocker	87(55%)	97(55%)	96(55%)	0.99
Diuretics	58(36%)	84(48%)	92(53%)	0.009
Statin	53(33%)	56(32%)	58(33%)	0.96
Vitamin K antagonists	151(95%)	169(97%)	167(96%)	0.76
Aspirin	7(4%)	5(3%)	5(3%)	0.67

Abbreviations: AF=atrial fibrillation; AFSS=AF Severity Scale; bpm=beats per minute; IQR=inter quartile range.
[a]Only applicable for strict rate control group.
[b]Normalized to metoprolol-equivalent doses.

Table 3. Specific AF-related symptoms as assessed by the AFSS and by the physician.

	Tertile 1 (N=174)	Tertile 2 (N=190)	Tertile 3 (N=194)	P-value
AFSS score	**0-3**	**4-9**	**10-35**	**for trend**
Components of the AFSS[a] – no. (%)				
No symptoms – no. (%)	45(26%)	-	-	-
Palpitations – no. (%)	30(17%)	105(55%)	165(85%)	<0.001
Dyspnea[b] – no. (%)	88(51%)	178(94%)	194(100%)	<0.001
Fatigue[b] – no. (%)	54(31%)	174(92%)	194(100%)	<0.001
Dizziness – no. (%)	28(16%)	71(37%)	153(79%)	<0.001
Chest pain – no. (%)	10(6%)	33(17%)	118(61%)	<0.001
Symptoms assessed by physician – no. (%)				
No symptoms – no. (%)	121(70%)	87(46%)	35(18%)	<0.001
Palpitations – no. (%)	15(9%)	33(17%)	82(42%)	<0.001
Dyspnea – no. (%)	21(12%)	56(29%)	121(62%)	<0.001
Fatigue – no. (%)	22(13%)	47(25%)	94(48%)	<0.001
Dizziness – no. (%)	3(2%)	8(4%)	18(9%)	<0.001
Chest pain – no. (%)	3(2%)	10(5%)	31(16%)	<0.001

Abbreviations: AF=atrial fibrillation; AFSS=AF Severity Scale
[a]Counts in table represent patients with AFSS score ≥1.
[b]In the AFSS each question relates to 1 specific symptom, except dyspnea and fatigue (symptom severity is questioned at rest and during exercise). We combined the scores on the rest- and exercise question for both symptoms.

Table 4. Endpoints per tertile of AFSS score.

	Tertile 1 (N=174)	Tertile 2 (N=190)	Tertile 3 (N=194)	
AFSS score	**0-3**	**4-9**	**10-35**	**P-value**
Primary endpoint	16(9%)	19(10%)	36(19%)	0.01
Death from cardiovascular cause	4(2%)	3(2%)	10(5%)	0.13
From cardiac arrhythmia	3(2%)	1(1%)	1(1%)	
From cardiac cause other than arrhythmia	1(1%)	0	2(1%)	
From noncardiac vascular cause	0	2(1%)	7(4%)	
Heart failure	4(2%)	1(1%)	16(8%)	<0.001
Stroke	3(2%)	4(2%)	5(3%)	0.93
Ischemic	2(1%)	4(2%)	3(2%)	
Hemorrhagic	1(1%)	1(1%)	2(1%)	
Systemic embolism	1(1%)	0	0	
Bleeding	6(3%)	6(3%)	12(6%)	0.28
Intracranial	0	2(1%)	1(1%)	
Extracranial	6(3%)	4(2%)	11(6%)	
Syncope	0	1(1%)	4(2%)	0.14
Life-threatening adverse effect of rate-control drugs	1(1%)	2(1%)	2(1%)	1.00
Sustained ventricular tachycardia or ventricular fibrillation	0	1(1%)	0	0.65
Cardioverter–defibrillator implantation	0	1(1%)	0	0.65
Pacemaker implantation	1(1%)	4(2%)	1(1%)	0.34
Secondary outcome				
Cardiovascular hospitalizations[a]	22(13%)	28(15%)	52(27%)	0.001

Abbreviation: AFSS=AF Severity Scale

[a]Cardiovascular hospitalizations consisted of syncope, life threatening adverse effects rate control drugs, sustained ventricular tachycardia or ventricular fibrillation, pacemaker implantation, implantable cardioverter defibrillation implantation (primary or secondary prevention), non life threatening adverse event of rate control drugs drugs, reveal implantation, hospitalization for chest pain without ACS, and hospitalizations for collapse without trauma, electrical cardioversion, pulmonary vein isolation and change in rate control drugs.

Association of AF symptom severity and outcome.

During follow-up, 71 patients reached the primary endpoint. Patients in the highest tertile of the AFSS score more often had heart failure hospitalizations (**Table 4**). Other components of the primary end point were not different between each tertile of the AFSS score. One-hundred-two hospitalizations for cardiovascular reasons occurred. More hospitalizations for cardiovascular reasons were observed in the highest tertile of the AFSS, mainly driven by heart failure hospitalizations. Kaplan-Meier curves for the primary endpoint and cardiovascular hospitalizations are shown in **Figures 1A** and **1B**, respectively. After multivariable adjustment, higher AFSS score was significantly associated with the primary endpoint (hazard ratio 1.38[1.15-1.66], p=0.001; **Table 5**),

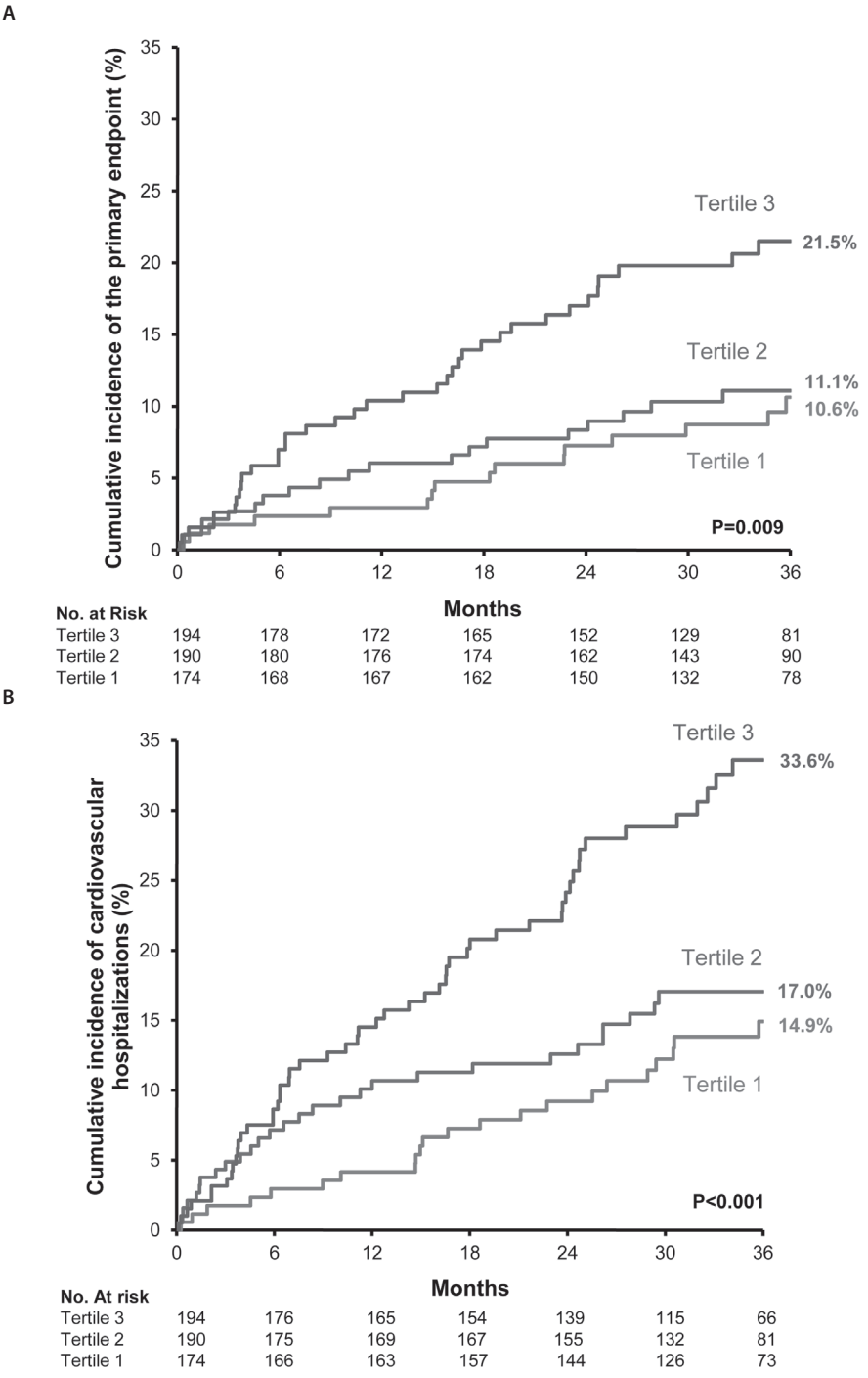

Figure 1. Kaplan-Meier estimates of the cumulative incidence of the primary outcome (**1A**), and cardiovascular hospitalizations (**1B**) according to tertiles of the AF Severity Scale (tertile 1=0-3, tertile 2=4-9, tertile 3=10-35).

as well as with cardiovascular hospitalizations (hazard ratio 1.33[1.14-1.54], p<0.001; **Table 5**). These associations persisted in almost all models when patients with previous heart failure hospitalizations (n=54) were excluded. However, the number of events were limited (n=58 for the primary endpoint, HR 1.35 [1.10-1.66], p=0.004, and n=87 for cardiovascular hospitalizations, HR 1.31 [1.11-1.55], p=0.002). Also for heart failure hospitalizations alone (n=21) multivariate analysis showed a significant association with AFSS (HR 1.69 [1.24-2.31], p=0.001). In contrast, presence of any symptom, and presence of palpitations, dyspnea and fatigue as assessed by the physician, was not related to the primary endpoint or cardiovascular hospitalizations (presence of any symptom: HR 1.20 [0.68-2.11], p=0.53 for primary endpoint, HR 1.20 [0.76-1.89], p=0.44 for cardiovascular hospitalizations).

Table 5. Association of AFSS (per 5 points) with the primary endpoint, and cardiovascular hospitalizations.

Endpoint	Model	Hazard ratio (95% CI)	P-value
Primary endpoint	Model 1	1.27(1.07-1.52)	0.008
	Model 2	1.26(1.06-1.51)	0.009
	Model 3	1.25(1.04-1.49)	0.016
	Model 4	1.38(1.15-1.66)	0.001
Cardiovascular hospitalizations	Model 1	1.30(1.12-1.50)	<0.001
	Model 2	1.29(1.12-1.49)	0.001
	Model 3	1.29(1.12-1.49)	0.001
	Model 4	1.33(1.14-1.54)	<0.001

Model 1: Age, sex, randomized treatment, previous hospitalization for heart failure, hypertension, diabetes, history of stroke adjusted
Model 2: Age, sex, randomized treatment, $CHADS_2$, coronary artery disease, valvular disease, heart rate >100 beats per minute adjusted
Model 3: Age, sex, randomized treatment, $CHADS_2$, betablocker, verapamil/diltiazem, ACE-inhibitors and/or angiotensin receptor blocker, diuretics at the end of the dose adjustment phase adjusted
Model 4: Age, sex, randomized treatment, $CHADS_2$, left ventricular ejection fraction, NT-proBNP, creatinin adjusted

Abbreviations: AF=atrial fibrillation; AFSS=AF Severity Scale; $CHADS_2$=stroke risk index (NYHA functional class II/III at baseline, hypertension, age >75 years, diabetes, and history of stroke); CI=confidence interval; NT-proBNP=N-Terminal prohormone of brain natriuretic peptide.

DISCUSSION

In the present analysis we found that patients with higher AFSS scores had more (signs of) heart failure, and were more frequently women. Higher AF symptom severity scores were associated with worse cardiovascular outcome, mainly driven by hospitalizations for heart failure. The presence of symptoms *per se* was not related to outcome.

Prevalence of AF-related symptoms and AF symptom severity.

Patients with permanent AF have less symptoms compared to patients with paroxysmal or persistent AF.(2,6,9) The prevalence of AF symptoms in RACE II is comparable to the prevalence reported from other permanent AF populations.(6,9) The mean AFSS score of 7.8±6.3 in our study including patients with short-lasting (<1 year) permanent AF was lower than in patients with symptomatic recurrent persistent AF (mean AFSS score >15) who were treated with amiodarone in the Continuous versus Episodic Prophylactic Treatment with Amiodarone for the Prevention of AF (CONVERT) trial.(16,17) This difference can be explained by differences in the patient populations. Patients in CONVERT had persistent AF, being still in a rhythm control strategy and were selected based on their symptomatology. In contrast, patients in present study had permanent AF, mild to moderate symptoms, and were candidates for a rate control strategy.

AF symptom severity and heart failure.

Patients with the highest AFSS scores had higher NT-proBNP and more previous hospitalization for heart failure and more often used diuretics, but there were no differences in other drugs used for heart failure treatment (beta-blockers, ACE-inhibitors and/or angiotensin receptor blockers). This suggests that AF patients with the most severe AF-related symptoms have more severe underlying heart disease, such as heart failure.(18) Presence of underlying heart disease could influence and aggravate AF symptoms. Of note, next to systolic left-ventricular dysfunction, diastolic left-ventricular dysfunction may be an important cause of heart failure in present cohort. Presence of AF may further impact impaired diastolic filling and lead to more severe AF-related symptoms.(19) Data from the RAte Control versus Electrical cardioversion for persistent atrial fibrillation study (RACE) study and from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study, showed that severity of underlying heart disease was associated with overall AF symptoms.(2,12,20) Prior analyses of the RACE II investigators already demonstrated that not the stringency of heart rate control influenced quality of life, but factors like the severity of the underlying disease.(10,21)

AF symptom severity and female sex.

In agreement with data from other studies we also found that women had more severe AF related symptoms, without one specific symptom driving the higher AFSS scores.(3,7,10,22) The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle study (FRACTAL) study demonstrated that AFSS is increased in women and patients with comorbidities, and is reduced in patients of older age.(23) Similar results were found in the Euro Heart Survey.(24) Several explanations for sex differences in AF symptomatology are possible. Firstly, differences in comorbidities between women and men may be one of the reasons.(22,25) In general, hypertension and diastolic dysfunc-

tion are more common in women than men.(25) However, prevalence of hypertension did not differ between AFSS tertiles, neither did bloodpressure. Secondly, sex-related differences in coping, symptom expression and illness burden could explain why women are more symptomatic than men.(26) A previous analysis from RACE II showed that female sex was associated with worsening mental health during follow-up independent of symptom presence.(10) Women may also seek medical attention earlier when they experience symptoms, and may be more prone to depression and anxiety.(27)

AF symptom severity and prognosis.

We demonstrated that symptom severity was, after multivariable-adjustments, associated with cardiovascular outcome, mainly driven by hospitalizations for heart failure. This relation persisted after exclusion of patients with previous heart failure hospitalizations. A prior analysis from the AFFIRM study showed that presence of symptoms was not associated with cardiovascular outcomes.(2) Symptom severity, however, was not evaluated in that study. Furthermore, the AFFIRM population consisted of persistent and paroxysmal AF patients, in contrast to our study.

Several scoring systems have been developed specifically for AF-related symptoms.(15,28,29) The present analysis of the RACE II trial evaluated the association of AF symptom severity with cardiovascular outcomes. Whether this relationship is caused by a direct effect of symptom severity on cardiovascular outcome, or whether symptom severity is marker of severity of disease is uncertain. In the multivariable adjusted models, the hazard ratio was not attenuated and the association remained statistically significant, also after adjustment for (markers of) left ventricular dysfunction. The clinical profile of patients in the highest AFSS tertile is different, and the AFSS score may act as a marker of underlying cardiovascular disease, and thereby be associated with impaired prognosis. This is supported by differences in the use of medication (rate control drugs and diuretics) at baseline and during follow-up and the fact that patients with the most severe symptoms, had more previous hospitalizations for heart failure, higher NT-proBNP concentrations, and shorter exercise durations, and used more often diuretics. However, patients in the lowest AFSS tertile more often used no rate control drugs or beta-blocker therapy alone, while the most symptomatic patients more often used the combination of digoxin and verapamil. We can, therefore, not exclude that adverse drug effects also may have influenced AFSS scores. There were no differences in achieved heart rate targets, dosages of individual rate control drugs, and number of dose adjustments visits between the tertiles of the AF symptom severity score, suggesting that the stringency of rate control did not influence outcome in the three groups. Clearly, what precisely caused symptoms and symptom severity in the individual patient warrants further investigation.(30)

AFSS score and relation with physician-documented symptoms.

An interesting observation is that when symptoms were assessed by the physician, a large proportion of patients (70%) in the lowest tertile of the AFSS, who reported mild symptoms on the questionnaire, were classified as asymptomatic. In addition, the most symptomatic patients according to the AFSS had relatively few individual symptoms as assessed by the physician. It seems that self-reported standardized symptom severity scores are more sensitive than history taking by the treating physician. Current guidelines recommend systematic use of the EHRA score.(1,31) Being a simple quantification score for AF related symptoms, the EHRA score may be even more applicable as compared to the AFSS score. This warrants future investigations.

Limitations.

The present study was a post-hoc analysis, and was not designed to determine differences in outcome in patients with permanent AF stratified by symptom severity, and study cause-effect relations. Therefore, we cannot definitely answer the question whether AF symptom severity *per se* is directly related to impaired prognosis, or whether it is a marker of more severe cardiac disease. Echocardiographic diastolic dysfunction parameters were not collected in RACE II, and non-cardiovascular conditions that were not systematically accounted for may also have determined AF symptom severity.

Potential implications.

The AFSS may be a useful and easy to perform questionnaire, to select patients at risk for future cardiovascular events, especially heart failure hospitalizations. This was recently demonstrated in a randomized controlled trial showing that weight reduction plus intensive risk factor management strategy led to a reduction in AF symptom burden and severity.(32) Future studies across the spectrum of AF subtypes are warranted to evaluate the use of AFSS as risk predictor and outcome measure, thereby improving personalized medicine.(30)

CONCLUSIONS

In the present post-hoc analysis of RACE II, we observed that after multivariable adjustment symptom severity as assessed with the use of the AFSS is associated with cardiovascular outcome in patients with permanent AF.

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Chapter 7

Obesity is Associated with Impaired Left Atrial Function in Young Patients with Recent Onset Atrial Fibrillation

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Obesity is a risk factor for atrial fibrillation (AF).(1) However, the exact pathogenesis underlying this association is unknown. We investigate the relation between obesity and left atrial function, measured with echocardiographic strain analysis, in young patients with recent onset AF.

We studied 89 patients of the Phenotyping Young-Onset Atrial Fibrillation Patients (Young AF) study. The Young AF study is a single-center observational prospective study performed in a tertiary referral center. Consecutive patients with an AF history <3 years who developed AF before age 60 years and with sinus rhythm during echocardiography were included in the present analysis. The institutional review board approved the study protocol. All patients gave written informed consent. Detailed clinical information was collected. All patients underwent a standard two-dimensional transthoracic echocardiogram (General Electric Vivid E9) during continuous ECG monitoring. Left atrial strain was measured using speckle tracking by two observers. Three strain-patterns (reservoir, activation, and conduit strain) representing left atrial functional phases were measured.

Of the 89 patients, 30 were obese (body mass index >30 kg/m^2) and 59 were non-obese (34±3 vs. 25±2kg/m^2, p<0.001; **Table**). There were no differences in median age, male sex, paroxysmal AF, total history of AF, hypertension, previous myocardial infarction, heart failure or previous stroke. However, diabetes mellitus was more common in obese patients (4[13%] vs. 1[2%], p=0.042). Left atrial volume indexed for body surface area, left ventricular mass indexed for body surface area, left ventricular ejection fraction and E/Et were not significantly different between obese and non-obese patients. However, the left atrial reservoir function (28±6 vs. 32±9%, p=0.020) was significantly reduced in obese patients. The left atrial activation strain and conduit strain were not statistically different between obese and non-obese. Using univariate linear regression analysis, there was a significant association between body mass index and all 3 strain patterns (**Figure**). In multivariate analysis adjusting for the baseline difference in diabetes mellitus and other relevant covariates (age, sex, hypertension, heart failure, myocardial infarction, left atrial volume index, left ventricular mass index, E/Et) the association between body mass index and reservoir strain (beta=-0.271, R=0.468, p=0.036) remained significant. Conduit strain (beta=-0.254, R=0.459, p=0.051) and left atrial activation strain (beta=-0.145, R=0.475, p=0.257) were not associated with body mass index in multivariate analysis.

We found that in young patients with recent onset AF, obesity is associated with impaired left atrial reservoir function, without differences in atrial volume. Reservoir strain was lower in both AF groups than in a previous report in healthy controls (45.5±11.4%).(2) The mechanistic link between obesity and atrial remodeling is multifactorial, and includes direct pro-fibrotic effects of epicardial adipose tissue,(3) fatty infiltration of atrial myocardium,(4) but also shared risk factors such as hypertension, diabetes mellitus and obstructive sleep apnea syndrome.(5) It has been previously shown in non-AF

Table: Patient characteristics.

Characteristic	Obese (n=30)	Non-obese (n=59)	P-value
Age–years	51(47-55)	53(45-56)	0.22
Male sex	17(57%)	42(71%)	0.17
BMI–kg/m^2	34±3	25±2	<0.001
Paroxysmal AF	25(83%)	48(81%)	0.82
Total history of AF	1.5±0.9	1.4±1.1	0.73
Diabetes mellitus	4(13%)	1(2%)	0.042
Hypertension	16(53%)	20(34%)	0.08
Myocardial infarction	3(10%)	1(2%)	0.11
Heart failure	-	3(5%)	0.55
Previous stroke	2(7%)	2(3%)	0.60
Echocardiograpy			
LA volume index (ml/m2)	30±9	30±8	0.84
LV mass index (g/m2)	83±19	77±16	0.11
LV ejection fraction (%)	58±3	58±3	0.96
E/e'	7(6-7)	6(5-7)	0.16
LA reservoir strain (%)	28±6	32±9	0.020
LA activation strain (%)	11±4	13±5	0.13
LA conduit strain (%)	17±6	19±7	0.09

Mean±standard deviation, median (interquartile range) or numbers (%). Abbreviations: AF=atrial fibrillation; BMI=body mass index; LA=left atrial; LV=left ventricular.

populations that left atrial function may be impaired in the presence of comorbidities before atrial dilatation occurs.(6,7) A previous study in a population with a longer history of AF (mean AF duration 5 years) showed that atrial function was reduced in obese patients compared to patients with normal weight.(8) However, no adjustment were made for baseline differences in comorbidities. Our results indicate that even in young patients with recent onset AF, obesity is independently associated with impaired left atrial reservoir function. Of interest, recent data showed that weight loss did not only reduce AF burden, but also reduced cardiac remodeling and pericardial adipose tissue on magnetic resonance imaging.(9) These findings may have the greatest clinical consequences in young early-AF patients, in whom further atrial remodeling and hence AF progression may be prevented.(10)

Our data show that early signs of atrial remodeling, without atrial dilatation yet, are present in obese patients independent of other AF risk factors. This again stresses that future research on improvement of rhythm control therapy should also embrace lifestyle changes including weight reduction in obese patients, instead of concentrating only on pharmacological and non-pharmacological therapeutic approaches.

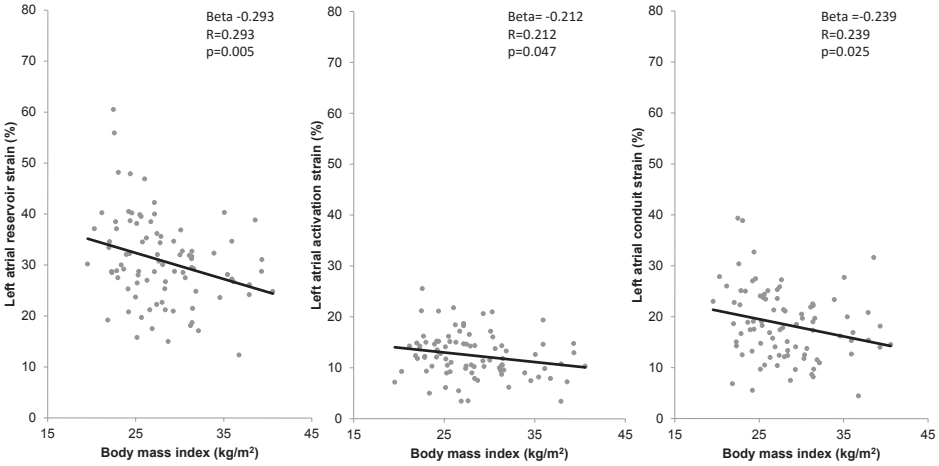

Figure. Association between body mass index and left atrial strain measurements, using univariate linear regression analysis.

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Chapter 8

Discussion and future perspectives

DISCUSSION

The general aim of this thesis was to uncover associations of underlying diseases and triggers with incident AF and AF progression in contemporary AF populations. In **Chapter 2** we found that the incidence of AF in a contemporary cohort in the Netherlands was 3.3 per 1000 person years which is comparable to data of older, mainly North American studies (3-19 per 1000 person years).(1) Of interest, obesity next to well-established risk factors, nowadays has become a major risk factor for incident AF. We now confirmed the association of incident AF with cardiovascular events, although overall event rates were lower than in older studies. In **Chapter 3**, we discussed the findings by Soliman and colleagues who found that AF was associated with a 63% increase in risk of myocardial infarction (non-ST elevation myocardial infarction).(2) These findings underscore the need for a detailed search for underlying risk factors for AF, such as vascular disease. In **Chapter 4** we found that young AF patients more often were men, and had less hypertension and diastolic dysfunction than older patients.(3) However a familial component was more frequent in young patients. Lone AF was very rare, even in these young AF patients. In **Chapters 5 and 6** patients with symptomatic persistent or permanent AF, respectively included in the RACE and RACE II studies were more often women and had more cardiac disease.(4,5) Symptoms were associated with worse cardiovascular outcomes.

As we demonstrated, obesity is becoming increasingly important as an AF risk factor, and may lead to atrial remodeling and hence worse outcome. In **Chapter 7** we studied the association between obesity and atrial remodeling. We showed that in young patients with recent onset AF, obesity is associated with impaired left atrial function, without differences in atrial dilatation.(6) Our results suggest that left atrial dysfunction may occur before dilatation occurs, and may hence be an early prognostic marker.

PART I: RISK FACTORS FOR INCIDENT AF

AF incidence.

Prospects report that with the ageing population AF will affect 17.9 million people in Europe by the year 2016, and 6-12 million people in North-America by the year 2050.(7-10) In **Chapter 2**, we found that the overall incidence rate of AF in a contemporary population in the North of Netherlands was 3.3 per 1000 person years.(1,11) As reported in other cohorts AF incidence was higher in men than in women, and there was a strong increase with age.(8,9,12-16)

The incidence was lower than observed in the Rotterdam Study, also a study from the Netherlands, where the overall incidence rate of AF was 9.9 per 1000 person years.

This may relate to age differences of included individuals (in Rotterdam Study mean age 69 years, in PREVEND mean 49 years); regional lifestyle related differences between the relatively large city of Rotterdam and the smaller city of Groningen;(15) earlier start of the Rotterdam study (inclusion 1990-1993, follow-up until 2000) than PREVEND (inclusion 1997-1998, follow-up until 2009);(1,15) and the fact that the Rotterdam Study also used data from general practitioners, which may have yielded additional AF cases, especially elderly.(15)

Likewise, populations describing AF incidence outside of the Netherlands were also of older age than the PREVEND population (mean age 55-73 years).(8,9,12-14,16-19) Like the Rotterdam Study, most of these studies followed their patients to the 21st century,(9,13-15,19) except for the Framingham Heart Study (inclusion 1948-1971, follow up until 2008),(12,16,17) and the Women's Health Initiative (inclusion 1994-1998, follow-up until 2007)(18).

Study visits at an outpatient clinic, as performed in our study, may provide better detection of AF and comorbidities than studies that rely solely on other means of AF detection, such as hospital visits or discharge codes.(8,12-17) Nevertheless incidence rates found in cohort studies using other means of AF detection and follow-up are often similar (2-12 per 1000 person years) (8,9,18,19) to those found in studies performing study visits (3-19 per 1000 person years).(8,9,18-20)

Continuously improvements are made in the treatment of cardiovascular risk factors for AF including hypertension, coronary heart disease, and heart failure.(21-23) Whereas improved treatment of cardiovascular diseases may reduce the risk of incident AF, on the other hand improved life expectancy and increasing prevalence of obesity and other lifestyle changes may increase the incidence of AF.(16) Risk factor management adapted to the changes in underlying disease may possibly improve prevention of AF.

AF risk factors.

Risk factors for incident AF are changing. Most data on comorbidities associated with AF in the general population have been obtained from old American cohorts starting their inclusion before the introduction of contemporary treatments for myocardial infarction, hypertension and heart failure, and increasing availability of diagnostic tests, and changing lifestyle.(21-24) Recent data show that while the influence of traditional risk factors on incident AF are decreasing, obesity and, possibly as a consequence, diabetes mellitus are gaining significance over the past decades. In **Chapter 2** we found similar associations of traditional risk factors with incident AF as compared with previous data.(1)

Next to these well-established risk factors, obesity was an important contributor to AF risk. Obesity often co-exists with other cardiovascular risk factors and diseases (e.g. diabetes, metabolic syndrome), and the sleep apnea syndrome. However, obesity by itself

may also induce AF (**Figure 1**).(18,25) It has been shown that epicardial fat may directly induce atrial fibrosis, and may even infiltrate the atrial myocardium.(25-29) Importantly, obesity is a modifiable risk factor, and recently it was shown that strict weight reduction significantly decreased the AF burden and atrial remodeling.(26,30-32) In **Chapter 2** the population attributable risk of obesity provided an indication that 9% reduction of incident AF could be achieved if the risk factor obesity could be completely removed from the population.(1)

Bidirectional relation of atrial fibrillation and myocardial infarction.

It is well known that myocardial infarction increases the risk of incident AF.(22) Conversely, recent studies suggest that AF is also associated with incident myocardial infarction, as was discussed in **Chapter 3**.(2,33-35) The most recent of these studies described the association of AF with myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study.(33) AF was associated with a 63% increase in risk of myocardial infarction (predominantly NSTEMI) after multivariable adjustments. The analyses in other cohorts by the same authors did not elaborate on the type of myocardial infarction (i.e. NSTEMI vs. STEMI).(34,35) As was observed in the analyses in other AF cohorts, women had higher risks of developing myocardial infarction, than men.(34,35) As discussed in **Chapter 3** there may be multiple explanations for these findings.(2) These include use of high-sensitive troponin assays in recent years, which have improved detection of minimal myocardial damage. Myocardial infarction, especially NSTEMI, is therefore diagnosed more often than before, and may even represent small myocardial damage as result of AF itself rather than result of atherosclerosis and significant coronary artery disease.(36) Myocardial infarction may also be caused by AF through increased heart rate and increased oxygen demand, sympathetic activation, endothelial dysfunction, and pro-inflammatory and pro-thrombotic effects.(37) Although AF and myocardial infarction share many risk factors, the association of AF and myocardial infarction may reflect on a final common pathway of underlying vascular disease.

Mechanistic ideas on the relation of AF and stroke may also be used to support this notion. A recent study among 187 patients with ischemic stroke during continuous monitoring by implanted devices showed that longer episodes of AF (≥5 hours) were temporally linked to the occurrence of stroke.(38) This fits Virchov's triad with low flow, increased plasma clotting factors and atrial wall abnormalities as a cause of thromboembolism. On the other hand data from 51 patients from the ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT) showed, in contrast, a temporal disconnect between stroke and continuously monitored occurrence of AF episodes >6 minutes.(39) Only 4 patients had longer lasting episodes (hours to days) within a 30 day period before the stroke, which may have caused the results to be statistically underpowered. Of note, atrial high rate

episodes >6 minutes were associated with stroke in the ASSERT study.(40) Results from these small studies should be viewed as hypothesis generating. Possibly, a temporal link between AF and stroke is only established after a threshold of arrhythmia duration, while a non-temporal association is caused by underlying vascular disease. This suggests that stroke, and probably also myocardial infarction, and AF have pathophysiological mechanisms in common. This is also reflected by the CHA_2DS_2-VASc score, the risk of

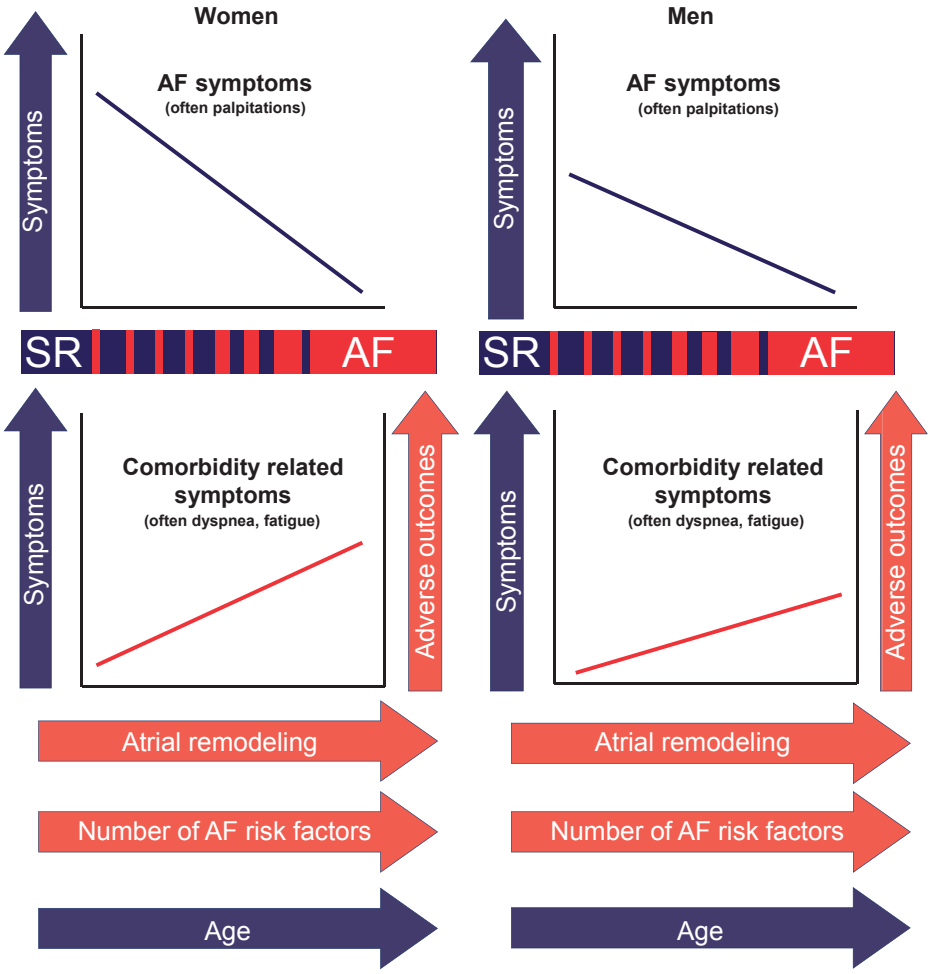

Figure 1. Conceptual figure of the association of typical AF related symptoms (often palpitations) and comorbidity related symptoms (often dyspnea or fatigue) with increasing AF chronicity, atrial remodeling, numbers of AF risk factors and age. No association exists between AF related symptoms and oucome. However comorbidity related symptoms are associated with adverse outcomes. Since AF-related symptoms and comorbidity related symptoms may overlap, clinicians should be aware of changes or increases of symptoms in individual patients. In general, women have more symptoms and, at older age, are at increased risk of adverse outcomes than men.

stroke depends on the number of cardiovascular conditions, and is higher in women at age >65 years.(41)

It has been speculated that older women with AF are at increased risk of stroke, through increased pulse pressure and worse blood pressure regulation compared to men, which is associated with endothelial dysfunction.(42,43) Pro-thrombotic factors have also been shown to be higher in women with AF than men.(42,44) Given the higher incidence of myocardial infarction in women with AF in the studies of Soliman et al.(34,35) it may be possible that mechanisms increasing the risk of stroke in women, may also increase the risk of myocardial infarction.(42,44)

Age differences in prevalence of AF risk factors.

In **Chapter 4** we demonstrated that compared to older patients, young AF patients were more often men, being taller, with less often hypertension, lower NT-proBNP and less signs of left atrial and ventricular remodeling and diastolic dysfunction.(3) Young patients had a higher prevalence of familial AF and cardiomyopathies. Compared to controls, young AF patients more often had hypertension and young AF men were taller. Obesity was highly prevalent in both age groups.

Male sex is a well established risk factor for incident AF, independent of associated comorbidities such as coronary heart disease.(22) The higher prevalence of men found in the young AF group of **Chapter 4** is consistent with data from population based studies, where younger AF patients were predominantly men.(3,8,17,45) This difference has been described to diminish with increasing age of the population.(8,17,45) Possibly, taller stature in men may contribute to the observed differences in sex distributions.(22) Anatomically larger atria are suggested as the main reason for an increased risk of AF in tall people. Reported risk increases for each 10 cm increase in height range from 1.3 to 1.6 fold.(13,14,46-50) This may relate to the fact that larger atria can host more reentry circuits.(51) One study evaluated lean body mass using dual-energy X-ray absorbometry, which was found to increase AF risk in post-menopausal women, independent of fat mass.(52) Data on left atrial size was not available in that study. The authors speculate that high body size (which is related to tall stature) may increase AF risk through effects other than adiposity, like larger atria, genetic predisposition or hormonal effects related to skeletal muscle.(52)

Differences in cardiac gene expression or influences of sex hormones between men and women could make men prone to AF at younger age, or alternatively protect young women from AF at younger age.(53,54) It has been described that electrophysiological differences exist between premenopausal women, post-menopausal women and age-matched men, that may possibly protect young women against AF through influence of sex hormones.(54)

Hypertension is one of the most prevalent risk factors for AF, both in men and in women, and its prevalence increases with age.(8,16,17,22) In **Chapter 4** the prevalence of hypertension in young AF patients was 41%, which was higher than in controls, but lower than in older patients, suggesting that even in young patients hypertension plays a major role in AF development.(3) Hypertension may lead to left ventricular hypertrophy and diastolic dysfunction, both of which have also been identified as AF risk factors.(22,55) LV hypertrophy and LV remodeling were present in 20% of young patients versus 40% in older patients, in conjunction with the prevalence of hypertension in both age groups.

Young patients also had better diastolic function, lower indexed atrial volumes, better atrial function and lower NTproBNP. The younger age itself and the lower prevalence of hypertension in young patients are the most likely contributors to these findings.(55) Still, atrial reservoir function was significantly impaired compared to controls in the literature suggesting the presence of atrial remodeling.(56,57) Both diastolic dysfunction and atrial remodeling are well known risk factors for AF.(22)

We also described that young onset AF is more often accompanied with a family history of AF and cardiomyopathies, than AF at older age. Previous studies have shown that family history of AF is associated with increased risk of developing AF, but also with younger age of AF onset.(58,59) Several genetic variants or mutations associated with AF have been identified.(60) These may directly lead to AF, but may also modulate the risk of developing AF through AF risk factors or cardiovascular disease.(61) Overlap exists between genetic variants and mutations associated with AF, and those found in cardiomyopathies or electrical cardiac diseases.(60,62,63) Young onset AF may be determined by genetic factors in greater part than in older AF patients, which is related to a higher prevalence of cardiomyopathies.

Genetic predisposition also seems to be involved in differences in AF risk across different ethnicities. Black individuals have more cardiovascular risk factors than white persons.(64) Nevertheless, white persons are at increased risk of AF after correction for other cardiovascular risk factors, in several populations worldwide.(13,14,50,64-66) In the ASSERT study even the unadjusted AF incidence rates were lower in blacks.(67) Interestingly, in African Americans, every 10% increase in European ancestry was associated with a 17% increase in the risk of incident AF.(64) Outcomes for African Americans with AF, however, are worse, possibly because of differences in lifestyle, higher prevalence of cardiovascular risk factors and disparities in AF treatment.(20) These differences between black and white Americans may also underlie the higher incidence of myocardial infarction after the diagnosis of atrial fibrillation in black individuals. African Americans were also shown to have the highest risk of in-hospital mortality during AF hospitalizations among all ethnic groups.(68) More research is needed to enable specific AF prediction in different ethnicities.

The prevalence of lone AF was very low in **Chapter 4**, even among young AF patients (2%).(3) It is still often believed that AF in young patients is accompanied with few, if any concomitant cardiovascular disease. As knowledge about new risk factors for AF increases, the question is raised whether lone AF may exist at al.(24,69,70) Systematic and thorough evaluation of young, seemingly 'lone', AF patients is therefore essential. (24,70)

PART II: RISK FACTORS FOR AF PROGRESSION

Prediction models.

AF progression is a continuum of atrial remodeling, increased AF chronicity and occurrence of cardiovascular events.(71) Underlying disease and comorbidities including age, sex, hypertension, heart failure previous stroke and vascular disease are the most important determinants of AF progression and AF related outcomes.(72-74) Risk prediction models that use these risk factors to estimate an individual's risk of morbidity and mortality are important to guide AF therapy. The most important adverse cardiovascular outcome of atrial fibrillation is stroke.(72-74) Several risk scores have been developed, most widely used are the $CHADS_2$ and CHA_2DS_2-VASc scores.(72-75) Although these scores are developed specifically for stroke, C-statistics are <0.70, meaning that a large proportion of the risk remains unexplained. Efforts are continuously being made to improve AF risk prediction, which has lead to a great variety of risk prediction schemes.(76)

The CHA_2DS_2-VASc score was shown to have comparable prediction of high stroke risk as other stroke risk schemes, including the $CHADS_2$,(77,78) 8th American College of Chest Physician Guidelines(79) and National Institute for Health and Clinical Excellence. (76,80) The strength of the CHA_2DS_2-VASc score, however, lies in better identification of patients at low risk for stroke, as compared to the $CHADS_2$ and other risk scores, enabling improved selection of patients requiring oral anticoagulation.(81,82) Other risk scores that have not yet reached daily clinical practice due to limited validation or less practical applicability are the R_2CHADS_2,(83) QStroke (84) and Atria Stroke Risk scores.(76,79) Still, adequate identification of patients requiring oral anticoagulation remains challenging, since patients treated with oral anticoagulation may be at risk of bleeding.(72-74)

Apart from stroke prediction schemes, scores assessing the risk of AF progression may further improve risk stratification. Progression from paroxysmal AF to permanent AF may occur with ageing and increasing numbers of concomitant conditions (and hence increasing $CHADS_2$ and CHA_2DS_2VASc scores)(**Figure 1 and 2**), (85-87) and is therefore associated with cardiovascular outcomes.(71,87) The HATCH scoring system, calculates 1 point for hypertension, age ≥75 years, chronic obstructive pulmonary disease, and 2 points for transient ischemic attack or stroke, and heart failure, allowing instant classifica-

tion of the risk of progression to persistent or permanent AF in patients with paroxysmal AF.(71) The studies that defined AF progression using clinical definitions (i.e. AF progression as assessed by the treating cardiologist) found reasonable predictive capabilities of the HATCH score.(**Table 1**) Interestingly, a recent study among 321 patients with dual-chamber pacemakers found that only a minority of patients showed progression of AF burden during a mean of 3 years of follow-up with continuous monitoring.(88) Only a diagnosis of heart failure, not the HATCH score, was predictive of AF progression.(88) Of course, results from a population with indication for dual-chamber pacemaker may not be generalized to the overall AF population. Possibly increased availability of continuous monitoring tools may soon help to improve prediction of AF progression in general AF populations.

Table 1. Studies describing prediction of AF progression by HATCH score.

	N	P	AF progression assessment	% AF progression	Mean HATCH	HATCH predictive ability
Sugihara et al. (2015)(88)	323	Dual-chamber pacemaker	Continuous monitoring	0.34% per year AF burden increase (3y FU)	1.7	NS
Chen et al. (2015)(149)	216	Succesfull atrial flutter ablation	24h Holter 3 and 6 mo, every 6 mo therafter	39% new onset AF after AFL ablation (2.5y FU)	2 in patients with AF 1 without AF	AUC 0.743
Potpara et al. (2012) (150)	242	Hospital based registry	Clinician	27% progression to permanent AF (assessed by clinician, 12y FU)	0.78	C-statistic 0.6
De Vos et al. (2010)(71)	1219	Hospital-based registry	Clinician	15% paroxysmal to persistent / permanent (assessed by clinician, 1y FU)	NA	AUC 0.675

Abbreviations: AF=atrial fibrillation; AUC=area under the curve; FU=follow-up; HATCH: risk score for AF progression, calculates 1 point for hypertension, age ≥75 years, chronic obstructive pulmonary disease, and 2 points for transient ischemic attack or stroke, and heart failure; N=number of patients; NA=not available; NS not significant; P=population; y=year.

Cardiovascular outcomes in the contemporary population.

In **Chapter 2** we found that incident AF was associated with a 2-fold increase of cardiovascular events including stroke, a 5-fold increased heart failure risk, and a 2-fold increased risk of all cause mortality, confirming the association of AF with cardiovascular events in a contemporary population.(1) Although the risks of events associated with AF were comparable to those found in other studies, overall event rates in the present study were lower than in older studies.(89,90) Compared to the Framingham Heart

Study, incidence of heart failure following incident AF was relatively low (18 vs. 33-43 per 1000 person years) (89), as well as mortality (30 vs. 51-74 per 1000 person years).(91) There are several reason why morbidity and mortality associated with AF was lower in our population. First, treatment of AF has significantly changed during the last decades. The most important change has been use of oral anticoagulation in individuals at risk for stroke, independent of preservation of sinus rhythm.(21) In addition improvements in oral anticoagulation have been made, further reducing the risk of stroke.(92-94) Second, beside anticoagulation use, treatment of other cardiovascular disease has also improved, which may have caused the further decline of event rates. For example fewer cardiovascular events occurred during follow-up of the RACE II study (95) (2005-2009) than in the RACE study (96) (1998-2001; **Figure 3**).

Although stroke prevention still is the cornerstone for improving AF related outcomes, the risk of heart failure and all cause mortality associated with AF should also be emphasized.(90)

AF and heart failure are strongly interrelated and have multiple risk factors in common. (22,72) In **Chapter 2** incident AF was associated with both heart failure with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF).(1) Limited data exists on the association of AF with the both subtypes of heart failure. Recent data suggest that men are at highest risk of developing HFrEF, while women are more likely to develop HFpEF, at older age than men.(97-99) This is most likely caused by differences in underlying disease such as more coronary heart disease in men and more hypertensive heart disease in older women.(97-99) A recent analysis in the PRVEND population showed that AF prevalent at baseline increased risk of HFpEF in women, but not in men. (98) On the other hand, the prevalence of HFrEF seems to decline, in part due to the excellent treatment of acute myocardial infarction.(100) The diagnosis of HFpEF in patients with AF, however, remains cumbersome,(101) possibly leading to underestimation of its incidence and prevalence. Overlap between (yet undiagnosed) HFpEF and AF symptoms may exist, predominantly in women, possibly leading to adverse outcomes because of undertreatment.

Although anticoagulation until now is the only AF treatment that has proven to reduce mortality (through reduction of thromboembolism), efforts are being made to find additional means of improving AF related survival. Although effects on mortality have not yet been published, strategies aiming on weight loss and improvement of cardiorespiratory fitness have shown promising results through reduction of AF burden and reverse atrial and ventricular remodeling (**Figure 4**).(27,30,32,102) Trials applying early contemporary rhythm control strategies that may improve cardiovascular outcomes are underway, and the results are eagerly awaited.(103,104) Next to stroke prevention and lifestyle changes, focus on prevention of heart failure and mortality in individuals with AF is important in the years to come, to further improve prognosis of those with AF.

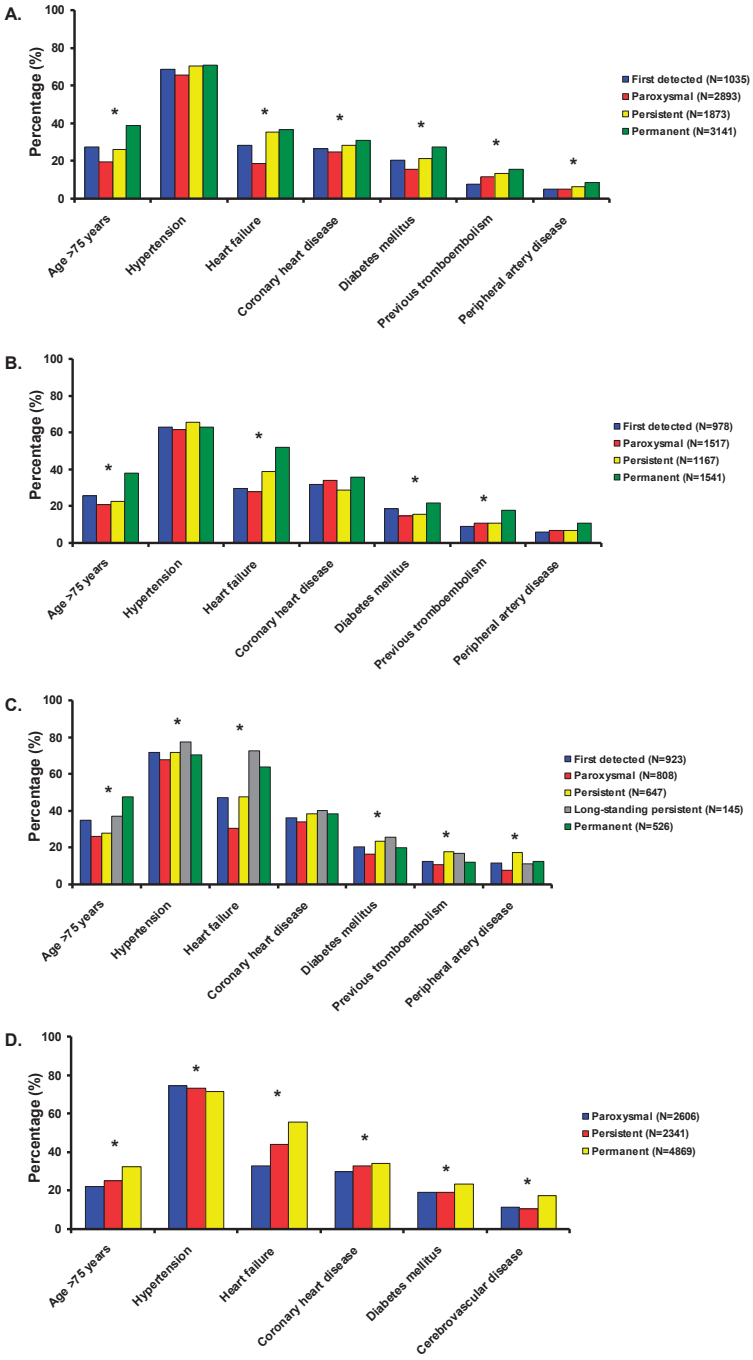

Figure 2. Prevalence of comorbidities according to different clinical AF types in the AF-NET registry(86) (**A**), Euro Heart Survey (106) (**B**), EORP-AF registry (113) (**C**), and RealiseAF registry (114) (**D**). The prevalence of comorbidities is greater in patients with persistent and permanent AF forms than in paroxysmal AF. *P<0.05

Symptoms as a marker of cardiovascular outcome in AF.

In **Chapter 5** we analyzed the clinical profile and outcome related to symptomatic persistent AF in the RACE study (**Figure 1**).(4) In **Chapter 6**, we investigated the clinical profile and outcome related to tertiles of the AF Severity Scale,(5) a validated AF symptom score in patients with permanent AF included in RACE II.(105) We showed that symptomatic persistent AF patients in the RACE study, and patients with permanent AF with higher AF symptom severity in RACE II, were more often women and had more severe cardiovascular disease, predominantly heart failure. Symptomatic AF or higher AF severity was associated with worse cardiovascular outcomes (**Figure 1**). This was driven by more heart failure hospitalizations in both studies, and adverse effects of antiarrhythmic and rate control drugs in the RACE study. No difference in the occurrence of thromboembolic complications was observed.

Symptoms and AF temporal patterns.

In general, patients with longer AF episodes (persistent and permanent AF) experience the least (overt) symptoms, while short-lasting paroxysmal AF episodes are most symptomatic (**Figure 1; Figure 3 of Chapter 1**).(86,106-110) Also, while dyspnea and fatigue are reported more by patients with longer more persistent AF episodes, palpitations are most common in patients with short, paroxysmal episodes (**Figure 1; Figure 3 of Chapter 1**). In **Chapters 5 and 6** we found that presence of symptoms in persistent AF, and increased symptom severity in permanent AF may be related to more severe underlying heart disease, predominantly heart failure, and worse cardiovascular outcomes.(4,5) A similar study was performed in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) population.(111,112) In AFFIRM, 60% of patients had paroxysmal AF, the thers had persistent or permanent AF. It was shown that symptomatic AF was associated with more severe cardiac disease, but relations with outcome were not significant.(111) Given the distinct relation of symptoms with different AF temporal patterns, the relation of symptoms with underlying disease, and therefore outcome may vary in different populations. Paroxysmal AF patients in general are highly symptomatic but often have less severe underlying disease.(86,106,113,114)(**Figures 1 and 2**) Since 60% of the AFFIRM population consists of paroxysmal AF patients, associations of symptoms with outcome may have been diluted.(4,111)

Several analyses investigating the association of AF symptoms with underlying disease and outcome were published from hospital-based AF registries.(108-110) Similar to AFFIRM, the majority of patients included in these studies had paroxysmal AF.(108-110) Symptomatic patients had more paroxysmal AF, younger age, were more often women, less often had underlying heart disease, and hence no relation of symptoms with worse outcome was found.(108-110) A recent meta-analysis found similar results.(115) However differences in AF temporal patterns between populations were

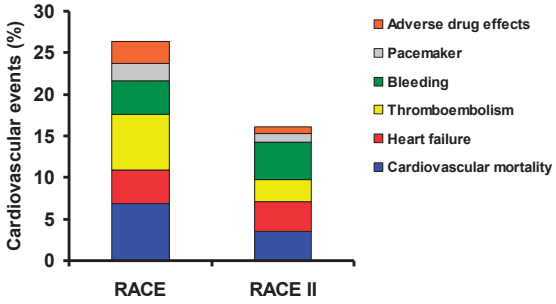

Figure 3. Incidence of cardiovascular events in the RACE (1998-2001; 522 patients, mean 2.3 years follow-up) (96) and RACE II (2005-2009; 614 patients, median 3 years follow-up) (95) studies.

not adjusted for.(115) In paroxysmal AF, symptoms may be driven by the arrhythmia itself rather than by the underlying heart disease (AF related symptoms, **Figure 1**).(86) Patients with persistent or permanent AF in general have less symptoms. However, a high symptom burden within persistent or permanent AF patients may point to more severe and possibly undertreated comorbidities (comorbidity related symptoms, **Figure 1**) and hence worse outcome.(4,5) Since AF-related symptoms and comorbidity related symptoms may overlap, clinicians should be aware of changes or increases of symptoms in individual patients and look for undertreated or new comorbidities.

AF symptom assessment.

Assessment of symptoms by the treating physician may, in part, be responsible for different relations of symptoms with underlying disease and outcome among populations.(40,106,111,116-121) Most studies report AF symptoms as assessed by the treating physician in a binary manner (yes / no), as was used in **Chapter 5**.(4,23,122) The 2010 European Society of Cardiology guidelines recommend classification using the European Heart Rhythm Association (EHRA) AF-related symptom score,(72,73) which has recently been validated and improved.(123) This score enables the physician to categorize symptoms according to severity. Still, assessment of symptoms by the treating physician may be less accurate than direct reporting by the patient. Therefore several scoring systems have been developed and validated specifically for AF-related symptoms, which enables the patient to accurately report symptoms.(23,122) These include the University of Toronto AF Symptom Severity Scale, the Symptom Checklist, and the Canadian Society Severity of Atrial Fibrillation Scale and the Atrial Fibrillation 6 Scale. (105,124-127) In **Chapter 6**, increasing severity of AF symptoms in permanent AF, assessed using the Toronto AF severity scale, was associated with more severe underlying disease and worse outcomes, similar to physician-assessed symptoms in **Chapter 5**.(4,5) Interestingly, when symptoms were assessed by the physician a large proportion of patients (70%) in the lowest tertile of the AFSS, who reported mild symptoms on the

questionnaire, were classified as asymptomatic by the physician (**Figure 5**). In addition, the most symptomatic patients according to the AFSS had relatively few individual symptoms as assessed by the physician. Similar findings were recently reported from the ORBIT-AF registry, where 11% of patients that were assessed as asymptomatic by the treating physician, reported mild symptoms on the Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT).(109) It seems that self-reported standardized symptom severity scores are more sensitive than history taking by the treating physician.

Whether the relationship of symptomatic AF and higher symptom severity with worse outcomes is caused by a direct effect on cardiovascular outcome, or whether symptoms are a marker of severity of disease (and predominantly [diastolic] heart failure) in persistent and permanent AF is uncertain. Clearly, what precisely causes symptoms and symptom severity in the individual patient warrants further investigation.(23)

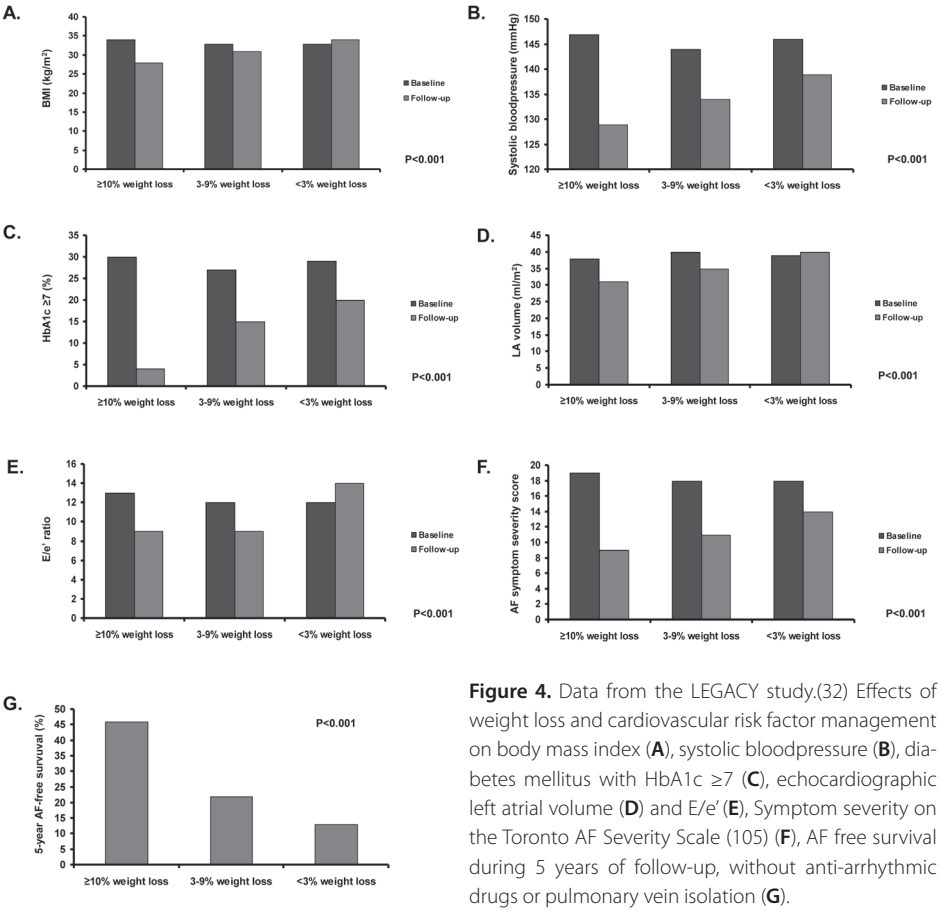

Figure 4. Data from the LEGACY study.(32) Effects of weight loss and cardiovascular risk factor management on body mass index (**A**), systolic bloodpressure (**B**), diabetes mellitus with HbA1c ≥7 (**C**), echocardiographic left atrial volume (**D**) and E/e' (**E**), Symptom severity on the Toronto AF Severity Scale (105) (**F**), AF free survival during 5 years of follow-up, without anti-arrhythmic drugs or pulmonary vein isolation (**G**).

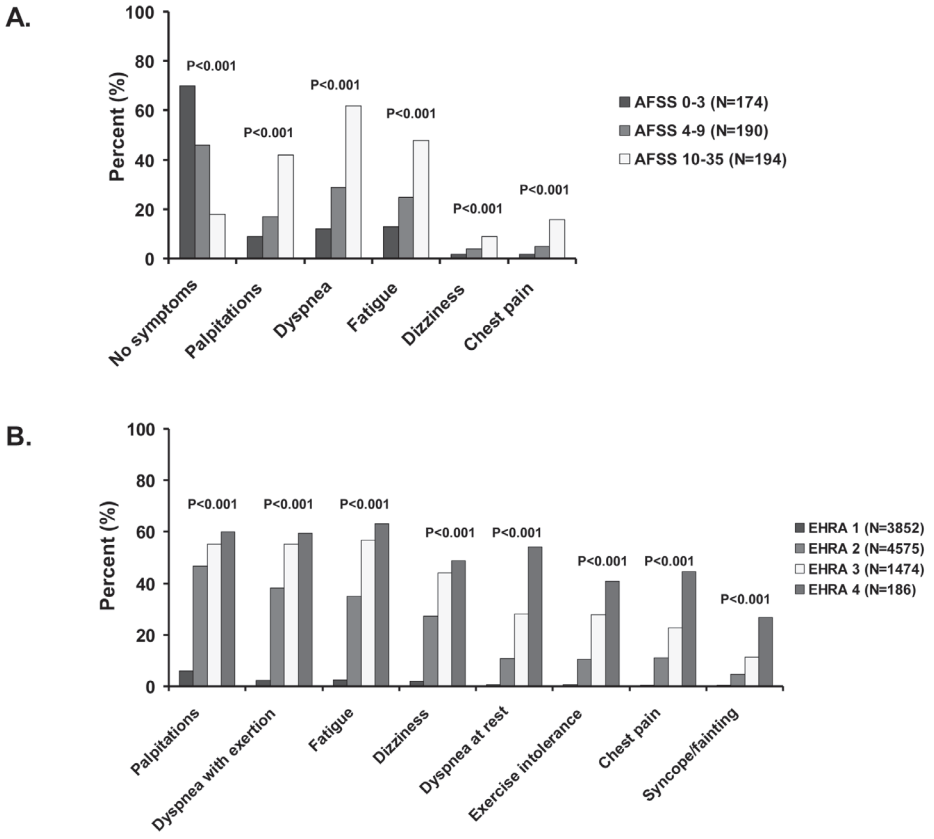

Figure 5. Specific AF-related symptoms as assessed by the AF Severity Scale and by the physician in **Chapter 6**(5) (**A**) and in the ORBIT-AF registry(109) (**B**).

Association of symptoms with female sex.

In **Chapters 5 and 6** (4,5) symptomatic AF was more common in women, at older age (**Chapter 5**),(4) was associated with more comorbidities and especially heart failure. It has been often described that women with AF are more symptomatic than men. (106-111,115,120,121) Whether this is caused by differences in age and comorbidities between men and women,(120,128) differences in disease coping and disease burden,(129) or differences in the incentive to seek medical attention,(130) is not completely understood.(131)

The relation of symptoms with underlying disease and predominantly heart failure in **Chapters 5 and 6** suggest that heart failure is an important determinant of symptomatic AF in persistent and permanent AF.(4,5) HFpEF and HFrEF were not separately defined in both studies. However, in **Chapter 5** symptomatic patients had more coronary heart

disease and more signs of systolic dysfunction on echocardiography, suggesting a higher presence of HFrEF in these patients.(4) Importantly, since the RACE study period (1998-2001) important improvements have been made in the treatment of myocardial infarction, reducing the overall prevalence of HFrEF.(100) In the more contemporary RACE II study (**Chapter 6;** 2005-2009) symptomatic patients more often had a previous heart failure hospitalization and had higher NT-proBNP, although no differences in systolic dysfunction were found, suggesting a high presence of HFpEF.(5,132)

Symptomatic patients in **Chapters 5 and 6** were more often women, and were older (**Chapter 5**) than asymptomatic patients.(4,5) Recent data shows that women develop heart failure at an older age than men, and more often have HFpEF rather than HFrEF. (97,120,128,133,134) AF and HFpEF frequently coincide, but HFpEF may be hard to diagnose, especially in patients with AF.(101) Possibly, the association symptoms, female sex, older age and adverse outcomes may be mediated through yet undiagnosed HFpEF. Indeed, our analyses in **Chapters 5 and 6** were adjusted for (among others) heart failure, coronary heart disease, systolic dysfunction on echocardiography and (in **Chapter 6**) NTproBNP, which did not attenuate the obeserved associations with outcome.(4,5) However no echocardiographic data on diastolic function was available. Clinicians should be aware of possible underlying HFpEF in symptomatic patients with persistent or permanent atrial fibrillation, especially in older women.

Effect of randomized treatment strategies on symptoms.

Theoretically, symptoms may be affected by differences in treatment strategy. The RACE study randomized patients with persistent AF to rhythm or rate control.(96) In RACE II, permanent AF patients were randomized to either strict or lenient rate control.(95) In **Chapters 5 and 6** no differences were found in AF treatment strategies between symptomatic and asymptomatic patients in the RACE and RACE II studies.(4,5)

Symptoms are an important determinant of quality of life, (119,121) Previous analyses from the RACE study showed that quality of life was similar between AF patients with long-term sinus rhythm (effectively treated with rhythm control), and AF patients with permanent AF (treated with rate control).(135) More recently, the RACE II investigators demonstrated that in patients with permanent AF, stringency of heart rate control did not influence quality of life, but that among others the severity of the underlying disease influenced quality of life.(121) In addition, no differences in quality of life were found when comparing permanent AF patients treated with successful strict rate control, unsuccessful strict rate control or lenient rate control.(136) In contrast to our studies, symptomatic patients in AFFIRM in the rate control arm more often underwent electrical cardioversion (although randomized to rate control) because of intractable symptoms. (111) It is likely that these patients were severely symptomatic paroxysmal AF patients,

although this was not further specified by the authors.(111) Nevertheless, in AFFIRM no differences in quality of life were seen between rate or rhythm control.(137)

New markers of AF progression

Development of underlying disease, increasing duration of AF episodes and development of cardiovascular events often go hand in hand with atrial remodeling in AF patients.(22) LA volume was associated with cardiovascular events and mortality in AF patients who otherwise had no overt cardiovascular disease.(138,139). However left atrial function may be impaired in the presence of comorbidities before atrial dilatation occurs, as an earlier marker of atrial remodeling.(140-147) A previous study in AF patients undergoing pulmonary vein isolation (mean AF duration 5 years) showed that left atrial function was reduced in obese patients compared to patients with normal weight.(146) However baseline differences in comorbidities were not adjusted for. In **Chapter 7** we reported that in young patients with recent onset AF, obesity was independently associated with impaired left atrial reservoir function, as evaluated with echocardiographic strain analysis.(6) Of interest, there were no differences in atrial size or atrial dilatation yet. Reservoir strain was also lower in both AF groups than in a previous report in healthy controls.(56) The mechanistic link between obesity and atrial remodeling is multifactorial, and includes shared cardiovascular risk factors, but also direct pro-fibrotic effects of epicardial adipose tissue and fatty infiltration of atrial myocardium.(27) Recent studies showed that weight loss did not only reduce AF burden, but also reduced cardiac remodeling and pericardial adipose tissue on magnetic resonance imaging.(31,32) As an early sign of atrial remodeling, atrial function may be associated with AF progression and cardiovascular events.(138) The prognostic relevance of impaired atrial function needs to be further established.

FUTURE PERSPECTIVES

With the changing epidemiology of AF, better prediction of incident AF and AF progression are needed. Obesity has gained importance as an AF risk factor in recent years, in both young and older patients (**Chapters 2 and 4**).(1,3) Aggressive strategies aiming on weight loss, cardiovascular risk reduction and improvement of physical fitness showed promising results in reductions of AF burden and improvements of atrial and ventricular remodeling, which offers huge opportunities for treatment of AF patients, when these strategies are incorporated in daily AF care.(30-32,102) However, inspiring patients to lose weight and to sustain lifestyle modifications is challenging, and requires highly motivated patients.(30-32,102) Relations of AF with (sub)clinical vascular disease are currently under investigation, which may provide additional risk stratification

tools.(**Chapter 3**)(2,148) Symptoms in persistent and permanent AF may also provide additional indications of the presence underlying disease and risk for cardiovascular outcomes (**Chapters 5 and 6**).(4,5)

Novel echocardiographic methods including echocardiographic strain analysis may provide additional mechanistic insights into atrial remodeling, which may enable early detection of patients at risk for AF progression and adverse outcomes (**Chapter 7**).(6) This may also apply to other cardiovascular imaging modalities including computed tomography and magnetic resonance imaging, which may provide important information on pericardial fat, atrial fibrosis, and possibly atrial function as well.(25)

Currently, inclusion in the Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (RACE 3) study is being finalized.(103) This study combines lifestyle management with an aggressive contemporary rhythm control approach, aiming to improve rhythm control and prognosis in patients with early AF and heart failure.(21,103) Other studies investigating whether contemporary AF treatment may improve cardiovascular outcomes are the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST)(104) and the Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA; ClinicalTrials.gov Identifier NCT00911508) Currently application of anticoagulants is the only treatment that has proven to improve prognosis.(77,92-94) Possibly state of the art rhythm control, including contemporary ablation strategies but also embracing lifestyle changes may be the next AF therapeutic strategy that improves AF prognosis.

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APPENDICES

Nederlandse samenvatting
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Biography

NEDERLANDSE SAMENVATTING (POPULAR DUTCH SUMMARY)

Atriumfibrilleren (AF) is de meest voorkomende hartritmestoornis. De verwachting is dat dit de komende jaren alleen maar zal toenemen. Ondanks verbeterde antistolling (directe orale anticoagulantia) zijn herseninfarcten de belangrijkste complicatie. Daarnaast leidt AF onder andere tot hartfalen, mortaliteit, dementie, verminderde kwaliteit van leven en hoge ziektekosten. In de afgelopen jaren is de behandeling van traditionele risicofactoren voor het ontstaan van AF, zoals hypertensie, hartfalen en hartinfarcten, sterk verbeterd. Maar de risicofactoren voor AF veranderen, doordat mensen steeds ouder worden en door de veranderende leefstijl. Naast het ontstaan van AF, leiden risicofactoren ook tot progressie van AF. Dit houdt in dat door verbindweefseling en verwijding van de hartboezems de duur van AF episoden en kans op complicaties toeneemt. Het in kaart brengen van nieuwe risicofactoren voor AF is daarom essentieel voor de behandeling.

Het doel van dit proefschrift is nieuwe risicofactoren voor het ontstaan van AF en AF-progressie te beschrijven. In **Hoofdstuk 1** wordt gestart met een algemene introductie op het thema van dit proefschrift. In **Hoofdstuk 2** beschrijven wij een analyse onder 8265 personen uit de bevolking van de stad Groningen. In deze moderne populatie hebben wij onderzocht bij hoeveel mensen nieuw AF ontstaat (incidentie), en hoe de relatie is met AF-gerelateerde complicaties. Naast traditionele risicofactoren voor AF, zoals hogere leeftijd, hypertensie en een doorgemaakt hartinfarct, blijkt obesitas in onze studie een belangrijke risicofactor te zijn voor AF. Verder bevestigt onze studie dat AF nog steeds leidt tot slechte uitkomsten, ook in een moderne patientenpopulatie.

Hartinfarcten zijn een bekende risicofactor voor het ontstaan van AF. Maar recent beschreven Soliman et al. dat AF ook een 63% hoger risico geeft op de het ontstaan van hartinfarcten. In **Hoofdstuk 3** bespreken wij deze bevindingen. Het is mogelijk dat het ontstaan van AF en hartinfarcten in dezelfde patiënten een uiting is van nog niet gedetecteerd, gegeneraliseerd vaatlijden. De bevindingen van Soliman et al. benadrukken dat het essentieel is voor de behandeling van AF om de onderliggende oorzaak te vinden (bijvoorbeeld vaatlijden).

Er is weinig bekend over risicofactoren voor AF in jonge patiënten, terwijl deze groep steeds meer voorkomt. In **Hoofdstuk 4** vergelijken we patiënten die op jonge leeftijd (<60 jaar) AF hebben ontwikkeld met oudere patiënten (≥60 jaar) en met controles zonder AF. Jonge AF patiënten zijn vaker man dan ouderen en hebben minder vaak hypertensie, maar vaker dan controles. Jonge patiënten hebben ook betere diastolische functie (ontspannen van de hartkamers), en minder aanwijzingen voor verbindweefseling van de hartboezems. Wel hebben jonge patiënten vaker AF in de familie en vaker hartspierziekten. Obesitas komt in beide groepen AF patiënten frequent voor (ongeveer

30%) en vaker dan in controles. Zelfs bij jonge patiënten komen risicofactoren frequent voor.

In **Hoofdstuk 5 en 6** onderzoeken we of aanwezigheid van AF-symptomen gepaard gaat met een ander risicoprofiel dan asymptomatisch AF bij respectievelijk persisterend en permanent AF. We vonden dat AF patiënten met aanwezigheid van symptomen en grotere ernst van symptomen meer onderliggende hartziekten hebben dan asymptomatische patiënten. De prognose van patiënten met (ernstiger) symptomen is ook slechter, wat vooral wordt veroorzaakt door meer ziekenhuisopnames voor hartfalen.

Ten slotte laten we in **Hoofdstuk 7** zien dat de functie van de hartboezems verminderd is bij jonge AF patiënten met obesitas, onafhankelijk van andere risicofactoren. Dit komt overeen met recente literatuur dat vetweefsel om het hart kan zorgen voor bindweefselvorming in de hartboezem. Verbindweefseling van hartboezems is gerelateerd met een slechtere prognose. Bij pogingen tot het herstel van het hartritme zou er meer aandacht moeten zijn voor gewichtsreductie bij obese AF patiënten. Mogelijk kan dit ook leiden tot minder complicaties van AF.

Tot slot worden in **Hoofdstuk 8** de belangrijkste bevindingen die in dit proefschrift zijn beschreven bediscussieerd en in de context geplaatst van de beschikbare wetenschappelijke literatuur over AF. Verder worden mogelijke nieuwe richtingen voor het verrichten van wetenschappelijk onderzoek gesuggereerd.

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BIOGRAPHY

Robert Aldo Vermond was born on October 7th 1984 in Heemstede, The Netherlands. After finishing his secondary education (Katholieke Scholengemeenschap Hoofddorp, Gymnasium, profile nature and health) he enrolled into Medical School at the Vrije Universiteit, Amsterdam.

During his study Rob was accepted for the Honours Programme, which sparked his interest in clinical research and cardiology, and ultimately led to two publications under the supervision of prof. dr. Hans Niessen and dr. Annemieke van Dijk. Further, Rob was active within the students' association 'Liber'. During his internships his interest in cardiology, as well as family medicine, increased.

After his graduation as a Medical Doctor in February 2010, Rob continued doing research with a PhD programme under the supervision of prof. dr. Isabelle van Gelder and dr. Michiel Rienstra in the University Medical Center Groningen. He presented his research in several international conferences, including the Scientific Sessions 2014 of the American Heart Association in Chicago, USA.

In 2014 Rob started as a resident in the cardiology department of the University Medical Center Groningen. Despite his interest in cardiology, he found that he would like to practice medicine in a more generalistic field. Since October 2015, Rob has been working as a resident in internal medicine in the Elisabeth-Tweesteden Hospital, Tilburg. In this position he gains additional experience for a future in family medicine. On June 10th 2016 Rob will marry Mirjam Brinkkemper.